External Control and Monitoring of Intravaginal Drug Delivery in Farm Animals

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by
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Abstract

Advances in cow estrus detection and synchronisation via controlled drug release will improve efficiencies in the dairy industry. To this end, this thesis describes the development, construction and testing of an advanced drug delivery, communication and monitoring system.

A weeklong trial with this system in five cows was conducted. The original aspects of the experimental work were: social grouping determined by inter-cow wireless communication; precise delivery of a pharmaceutical vehicle over short or extended periods of time for controlled delivery in accordance with a complex profile; external wireless control/override of delivery; and the ability to gather an array of different data at once from the cow vagina by wireless communication.

The conclusion was that external control and monitoring of controlled delivery in farm animals is possible and that future systems may extend the control/feedback loop outside the drug delivery device, the animal itself, and the farm at which the animal resides.

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Table of Contents

Abstract iii
Acknowledgements v
Table of Contents vii
List of Figures xi
List of Tables xv
Glossary xvii

1. INTRODUCTION 1

1.1 Overview 1
1.2 Thesis Objectives 2
1.3 Relationship With Industry 3

2. BACKGROUND 5

2.1 New Zealand Dairy Industry Structure 5
2.2 Current and Future Trends in the Global Dairy Market 7
2.3 Increasing Dairying Efficiency Through the Use of Controlled Drug Release 9
2.4 Estrous Control 14
2.5 Controlled Drug Release for Estrus Control 33

3. DEVELOPMENT OF A PRACTICAL DRUG DELIVERY, COMMUNICATION AND MONITORING SYSTEM 45

3.1 Introduction 45
3.2 Contemporary Controlled Drug Release Design Philosophy 46
3.3 Requirements of the Proposed Drug Delivery System 48
3.4 Overview of DMU Operation 50
3.5 Drug Delivery Control 53
3.6 Power Management 66

3.7 Communication 74
3.8 Executive Control 94
3.9 Environmental Monitoring 98
3.10 Software Design Methodology 104
3.11 Base Station 106
3.12 Construction 108
3.13 Bench Testing 111
3.14 Specifications 117

4. EXPERIMENTATION 119

4.1 Materials 119
4.2 Methods 120
4.3 Results and Discussion 124
4.4 Experimental Results Summary 144

5. DISCUSSION 145

5.1 Performance Assessment 145
5.2 Defect Analysis and Suggested Remedies 146
5.3 Critique of Design Process 148
5.4 Suggested Enhancements to Current System 148

6. CONCLUSION 155

6.1 Future Systems 155
6.2 Extending the Control Loop to the Organism 159
6.3 Remote Data Gathering From Many Sites 163
6.4 Integrated Estrus Detection 166
6.5 Conclusion 169

APPENDIX A: ADDITIONAL EXPERIMENTAL RESULTS 173

APPENDIX B: DMU SCHEMATICS 177

APPENDIX C: DMU PCB LAYOUT 185

APPENDIX D: DMU BILL OF MATERIALS 189

APPENDIX E: BASE STATION/DEVELOPMENT DMU 199

APPENDIX F: CD-ROM CONTENTS 207

REFERENCES 209

List of Figures

Figure 1: Anatomy of the Cow (Webster 1993, 2) 15
Figure 2: Cow Reproductive Process: Follicle Development and Degeneration (Webster 1993, 2) 17
Figure 3: Application of CIDR® to Bovine Estrous Cycle (InterAg 2000) 38
Figure 4: SMARTT1® Intelligent Breeding Device (Plade Holdings 1999) 39
Figure 5: System Overview 51
Figure 6: Block Diagram of Delivery and Monitor Unit (DMU) 52
Figure 7: Gascell Physical and Schematic 54
Figure 8: Sample Delivery Profile Defined on PC for Download into DMU 55
Figure 9: DMU Gascell Switch Decision 60
Figure 10: Gascell Monitor Physical and Schematic 64
Figure 11: Power Mode Control 69
Figure 12: Transceiver Hybrid Physical and Schematic 79
Figure 13: Amplifier Sequenced Hybrid Transceiver Block Diagram (RF Monolithics Inc. 2001) 80
Figure 14: Receiver Signal Processing (RF Monolithics Inc. 2001) 85
Figure 15: Air Interface Packet Structure 88
Figure 16: Mitsubishi M16 Microcontroller Block Diagram (Mitsubishi Electric Corporation 2001) 96
Figure 17: Pressure/Temperature Sensor Physical and Schematic 99
Figure 18: Motion Sensor Physical and Schematic 100
Figure 19: Light Sensor Physical and Schematic 102
Figure 20: Base Station/DMU Communication Flow 107
Figure 21: DMU Electronics Construction 109
Figure 22: DMU Electronics Package Fitted to Modified Theratron© Syringe, Sectioned for Display and Shown Actual Size 110
Figure 23: Complete DMU Ready for Deployment 110

Figure 24: Volume and Pressure During Bench Test of Variable Rate Delivery..113
Figure 25: Volume and Volume Rate During Bench Test of Variable Rate Delivery 114
Figure 26: In vitro (□) and In vivo (■) Rate of Delivery (Bunt et al. 2001, 28) ...116
Figure 27: Removal For Inspection and Piston Position Check..... 121
Figure 28: DMU In Vivo 121
Figure 29: Location of DMU in Cow Adapted from (Webster 1993, 2) 122
Figure 30: Variable Rate Profile Used In DMU's 1 and 2 123
Figure 31: Sample Graph for Familiarisation 125
Figure 32: Downloaded Results: Temperature 127
Figure 33: Downloaded Results: Temperature in Frequency Domain 128
Figure 34: Flat Profile: Target, Estimated and Observed Drug Volume 130
Figure 35: Flat Profile: Target Integrated Current and Target Integrated Current Rate 132
Figure 36: Downloaded Results: Gascell Voltage and Current 133
Figure 37: Downloaded Results: Pressure, Temperature and Estimated Volume Delivered: Close-Up 135
Figure 38: Downloaded Results: Pressure, Temperature and Estimated Volume Delivered: Full Duration 136
Figure 39: Downloaded Results: Cow Proximity Recorded By DMU 3..... 137
Figure 40: Downloaded Results: Cow Proximity Recorded By DMU 1..... 138
Figure 41: Downloaded Results: Cow Proximity Recorded By DMU 2..... 138
Figure 42: Downloaded Results: Motion 139
Figure 43: Downloaded Results: Light Intensity 141
Figure 44: DMU Power Supply Voltages 142
Figure 45: Discharge Curve of Energizer EPX76 Silver Oxide Battery Adapted from EPX76 data sheet (Eveready Battery Company 2001) 143
Figure 46: Closed Loop Drug Delivery (Claycomb 2001) 162
Figure 47: Symbolisation of One Monitoring Site 164
Figure 48: Network for Remote Design and Monitoring of Drug Delivery Programmes..... 165
Figure 49: DMU Schematic: Top Level 178
Figure 50: DMU Schematic: Digital Board — Microcontroller..... 179

Figure 51: DMU Schematic: Digital Board — Power and Supervisory 180
Figure 52: DMU Schematic: Digital Board — Peripherals 181
Figure 53: DMU Schematic: Transceiver and Batteries Board 182
Figure 54: DMU Schematic: Programming Cable 183
Figure 55: DMU PCB Layer Stack Up 185
Figure 56: DMU PCB Layout: Digital Board Side 1 and Inner Layers 186
Figure 57: DMU PCB Layout: Digital Board Side 2, Power and Ground 186
Figure 58: DMU PCB Layout: Transceiver and Batteries Board Side 1 187
Figure 59: DMU PCB Layout: Transceiver and Batteries Board Side 2, Power and Ground Planes 187
Figure 60: Modified M16C Evaluation Board Schematic — Sheet 1 200
Figure 61: Modified M16C Evaluation Board Schematic — Sheet 2 201
Figure 62: Modified M16C Evaluation Board PCB Layout 202
Figure 63: Base Station/Development DMU 203
Figure 64: Modifications to DR3100 Transceiver Module 206

List of Tables

Table 1: Description of Microcontroller Modes 68
Table 2: Current Consumption in Sleep Mode 71
Table 3: Current Consumption in Fully Awake Mode 72
Table 4: Base Station Help Screen 92
Table 5: Logged Data Result Set 97
Table 6: User Requesting a Snapshot From DMU 4 Over Wireless Link 112
Table 7: DMU Specifications 117
Table 8: Description of Observations, Results and Manipulations for DMU 3 and Control Syringe 174
Table 9: User Requesting Setup Information From DMU 4 Over Wireless Link 175
Table 10: DMU PCB Specifications 185
Table 11: DMU Bill of Materials 189
Table 12: Development Board Cross Reference Wiring Table 204
Table 13: Jumper Settings for the M16C Microcontroller Evaluation Board 205

Glossary

AI	Artificial Insemination.
Anestrous	Non-cycling behaviour in non-human mammals in which the ovaries fail to exhibit follicular development and ovulation.
Anestrus	State or interval of sexual inactivity between two periods of estrus
CIDR®	A T-shaped intravaginal nylon spined insert which is coated with progesterone loaded silicone. The purpose of the device is to control the estrous cycle in cows.
Corpus luteum	An endocrine gland that forms once the dominant follicle in the ovary has released its egg under the influence of the lutenising hormone. The corpus luteum phase of the estrous cycle then regresses. In the pregnant animal, it remains active throughout pregnancy. The corpus luteum is destroyed by uterine secretion of prostaglandin $F2_{\alpha}$.
DMU	Delivery and Monitor Unit: The intelligent delivering, monitoring, and communicating drug delivery system developed for this project.
Estrous	The biological cycle regulated by the endocrine system that controls the physiological and behavioural aspects of a non-human mammal's reproductive system.
Estrus	Period of the estrous cycle during which the female is receptive to the male (heat). This is accompanied by behavioural and physiological changes in most animals.
Flash memory	Memory which retains program code and data even when power is removed. The M16C microcontroller used in this thesis has 256K of flash memory which can be re-written in blocks during program execution.
Gascell	The same size and shape as a button cell calculator battery, the gascell produces hydrogen when an electrical load is connected to it. Assuming other factors are constant, gas production is directly proportional to current drawn. The gascell is used in the Theratron® syringe to propel the drug vehicle.
MEMS	Micro Electro-Mechanical Structure. Chip-scale devices that can sense and/or control the physical environment.
RAM	Random Access Memory can be re-written in individual bits and bytes at high speed, but does not retain data when power is removed. The M16C microcontroller used in this thesis has 20K of RAM.

RFID	Radio Frequency IDentification. A system of identification whereby the item, animal or person to be identified carries a transponder. A reader interrogates the transponder with a coded radio signal and the transponder replies with a unique identification number.
Theratron®	A commercially available, purpose built, syringe incorporating a gascell. The gascell produces a constant supply of gas behind the syringe piston which provides controlled delivery of the pharmaceutical vehicle. Originally intended for human portable drug infusion, it was modified to form the basis of the drug delivery mechanism used in this thesis.

1. Introduction

1.1 Overview

A review of current and emerging estrus detection and drug delivery technologies was conducted in relation to the local dairy industry. This established a need for an investigative programme into external control and monitoring of controlled drug release in farm animals. This review provided the basis for a feasibility and design study for the device used for in vivo experimentation. Development, construction and testing of this practical drug delivery, communication and monitoring system was described.

This Delivery and Monitor Unit (DMU) was designed to evaluate intelligent variable rate controlled release in the cow vagina along with a data logging system for diagnostic and environmental information. Included is a two-way radio link for external control and exchange of information with the base station, and other cows, while in vivo.

Methods, materials and results from an experiment using the DMU in a weeklong trial involving five cows were presented. The original aspects of the experimental work were: social grouping determined by inter-cow wireless communication; precise delivery of a pharmaceutical vehicle over short or extended periods of time for controlled delivery in accordance with a complex profile (three percent accuracy with safety limit override); external wireless control/override of delivery; and the ability to gather an array of different data at once from the cow vagina by wireless communication.

An evaluation of the performance of the system identified it as meeting or

exceeding all of the initial design criteria. Discussion then followed on how this, and future systems, might be developed. Possible herd based and farm based systems were considered.

The conclusion was that external control and monitoring of controlled delivery in farm animals is possible and that future systems may extend the control/feedback loop outside the drug delivery device, the animal itself, and perhaps even the farm at which the animal resides.

1.2 Thesis Objectives

Drug delivery is a huge field. Even within the veterinary field of application, controlled drug release is a major focus of journals, regulatory bodies, discussion groups, and an even larger number of commercial products. This introduction establishes a need for pursuing the thesis objective of investigating external control and monitoring of intravaginal drug delivery in farm animals. A significant commercial application of the intravaginal route in dairy cows is for estrus control. Estrus detection and control are covered in detail because those topics motivate the development of experimental objectives in later chapters.

This scope provides an active topic large enough by itself, while allowing a focus on specific issues of application. Reference is made to the more general problem of drug delivery in humans and animals where appropriate.

Current demands from animal scientists include the need to deliver multiple drugs at different rates and amounts over extended time periods. Such demands are difficult to meet using conventional polymeric formulations. The use of electronically controlled drug delivery systems provides the pharmaceutical scientist with the opportunity to achieve these demands, however, much fundamental and applied work needs to be performed before these demands are met.

It is the aim of this thesis to provide fundamental information on the capabilities

of controlling electronic drug delivery systems thereby building on knowledge in this growing area of research. Specific objectives are to:

1. Examine the feasibility of electronically controlled intravaginal delivery in farm animals including the ability to externally control the delivery system.

2. Report on the methods for doing so, problems that might arise and the solutions to those problems.

3. Build a system capable of controlled release, external control and monitoring of intravaginal delivery in farm animals. The in vivo device should be able to precisely deliver pharmaceutical vehicles over short or extended periods of time according to a complex profile (rather than simply on/off or constant rate).

4. Assess and report on the performance, usefulness, capabilities, possible improvements and future applications of the system as built.

5. Suggest improvements for development of future systems.

6. Consider the implementation of a herd based system providing individual and collective data to a remote computer.

1.3 Relationship With Industry

InterAg is a research company specialising in intravaginal controlled drug release for estrous control in cattle. Sensortec, a sister company, develops in-line sensors for complex biological fluids. Both companies are based in Hamilton, New Zealand having forged strong bonds with The University of Waikato, Government funded research agencies and overseas collaborators from a variety of backgrounds.

Their relationships with universities focus on providing a source of interesting and worthwhile projects to which postgraduate students can apply themselves. This results in projects which are a mixture of pure research and commercially oriented content that prove mutually beneficial. The companies provide substantial

materials, resources and expert guidance. In return, they receive the benefits of the student's effort in exploring relevant new areas of research, backed by the rigour of academic supervision from the University.

The University itself gains a reputation for producing immediately employable graduates who have experience with real world problems and an appreciation of the underlying theory. This thesis is an example of this ongoing collaborative effort.

2. Background

2.1 New Zealand Dairy Industry Structure

Justification for research into the general problem of drug delivery in dairy cows for estrous control requires a brief understanding of the social and economic factors operating in the industry on a local and global scale. For this purpose, the current state of the New Zealand dairy industry is briefly described.

2.1.1 Ownership

New Zealand farmers own co-operative processing companies. By far the biggest of these is the newly created Fonterra company that accounts for 95% of dairy production.

2.1.2 Exporting

New Zealand, with four million people, does not have a large domestic market, and is forced to export the bulk of its production (96%). Because of this, New Zealand accounts for over 30% of the total volume of internationally traded dairy products, while it accounts for only 2% of the total world dairy production.

2.1.3 Farms

In 1999 New Zealand had a total of 14 400 dairy farms. In the last twenty years, the number of dairy farms has fallen, but the average farm and herd size has increased. Productivity per hectare and per cow have both been substantially improved. The majority of New Zealand dairy farms are owned and operated by farming families. In addition, there is an established share milking system, under

which a sharemilker is contracted to milk the herd and carry out a range of farm duties for a share of the milk income. This system promotes trained, eager young people into the industry and allows them to build equity before proceeding to farm ownership.

Most herds are milked in spring, summer and autumn, but dried off in winter when pasture production is lower. The rest of the herds supply milk year-round for the domestic liquid milk industry. The seasonal milk production system relies predominantly on highly productive, rotationally grazed pasture and herds of high genetic merit. The favourable climatic conditions eliminate the need for indoor housing and expensive feed supplements. This system enables farmers to produce milk substantially below the average world costs, giving New Zealand its advantage over competitors worldwide.

On farm technologies including artificial insemination for genetic improvement, newly improved pasture species and milk harvesting technologies have enabled New Zealand to remain a world leader in low cost milk production.

2.1.4 Current New Zealand Dairy Efficiency

New Zealand has a completely unsubsidised industry whose efficiency is commonly regarded as the highest in the world. The New Zealand dairy industry provides 1.3 billion kg of relatively low-cost product annually. On-farm cost of milk is estimated at NZ$2.80 per kg of milk solids, compared to Australia where it is NZ$4.00, and Europe and the US, where costs are at least NZ$6.50.

In 1986/87, the average full-time farm worker produced NZ$40 000 worth of farm produce. In 1995/96 this had risen to NZ $55 000 of produce per worker. This represents an increase of over 34% in real terms in labour productivity in agriculture compared with a productivity gain of 14% in real terms for the total New Zealand economy over that period.

While New Zealand dairy farmers are extremely efficient producers of milk, their net incomes have declined significantly over the last decade (Producer Board Project Team 1999).

2.2 Current and Future Trends in the Global Dairy Market

2.2.1 Global Competition

The decline in farm incomes is related to the fact that New Zealand has a continued reliance on low-margin commodity exports. While New Zealand milk output has increased significantly, this volume increase has been offset by falling commodity prices. With 70 percent of New Zealand dairy exports unbranded, New Zealand remains highly exposed to fluctuations in international commodity prices.

In 1999, Promar International UK was commissioned to write a report titled *International Forces Shaping The New Zealand Dairy Industry* by the New Zealand Ministry of Agriculture & Forestry and other government departments. This report claims that as domestic demand is essentially constant, New Zealand must look internationally to sustain growth (Promar International 2001). This will be difficult given that international competition is predicted to increase. According to this report, the New Zealand dairy industry will have to continue to develop these international markets if it is to maintain a competitively priced product.

On the plus side, there are some positive global influences that will take effect in the medium term. Under the agreed terms of the World Trade Organization, agricultural subsidies in other countries are to be phased out eventually. Because New Zealand has already totally abandoned subsidy of agricultural production, the country stands to gain when other countries remove their subsidies. Prices for New Zealand dairy exports can be expected to rise very substantially once this happens, however this could be a drawn out process.

Another positive trend is the international market for processed dairy products which is expanding in breadth and depth. In particular, yoghurt and flavoured milk have achieved very high growth on a global scale and the cheese market in Japan is small but developing. In the past, the Asian markets have been

considered poor, but there is a new dairy consuming generation reaching maturity in Japan. The Japanese Government has raised public awareness of the goodness of milk and subsidised it in schools for many years now. The same strategy is now being trialled in China. This will create a new dairy consuming generation in the world's most populous nation. Already the predicted growth of 20% per annum is being revised upwards; closer to 50%. While New Zealand has traditionally focussed on raw milk products, this gives it a huge potential for gain if it can capitalise on these value added markets and invent new ones along the way.

2.2.2 Global Trends Affecting the Industries

Future global decreases in price due to globalisation, biotechnology and increased efficiency in other countries means that the New Zealand dairy industry cannot rest on its laurels. It has been generalised that other countries' cost of producing milk solids is decreasing at a sustained rate of 2% per annum, while New Zealand's cost is rising at 2%. This is the basis behind the "Meeting the 4% challenge" campaign (Dexcel Ltd. 2001a) to make New Zealand dairy farmers realise that they must continually strive for increased efficiencies.

Current global trends affecting the profitability of New Zealand's dairy and related industries are (Producer Board Project Team 1999):

- Long term decline in commodity prices.
- Rising consumer food safety concerns.
- Demand for more product traceability.
- Retail consolidation.

Future additional costs may increase as a result of:

- The need to meet tougher environmental constraints such as reducing nitrogen run-off in local water ways.
- The impact of decisions regarding genetically modified organisms.

- The introduction of greenhouse gas taxes (methane emissions from animal digestion).
- Developments in e-commerce.
- Changing consumer preferences and practices.

2.3 Increasing Dairying Efficiency Through the Use of Controlled Drug Release

By reviewing past trends and future predictions, it has been established that the New Zealand dairy industry must continually strive for increased efficiencies if it is to remain successful. The application of controlled drug release to the estrous cycle can help in attaining increased efficiencies in the following ways.

2.3.1 Increased Spread of Processing Demands Throughout the Year

New Zealand dairy processors receive volumes of milk between 1% and 100% of peak milk flow. In comparison with Northern Hemisphere processing throughput, where processing throughput varies between 82% and 100% of the peak milk flow, this is a large seasonal variation. The global demand for milk products is spread, more or less, evenly throughout the year. As a result, the New Zealand dairy industry's processing facilities operate below optimum efficiency for large parts of the 12 month cycle. In addition, the requirement for increased storage to match supply with demand further adds to overall costs.

The ability to spread processing volume more evenly throughout the year to achieve greater efficiencies relies partly on a regionally co-ordinated calving cycle. Controlled drug release for the purposes of timing exactly when cows are inseminated throughout the season can pay dividends in this area if spreading were to be actively pursued. Unfortunately, being pasturally based, there is a hard limit to which this spread of milk solids output can occur in New Zealand.

2.3.2 Compact Calving

Compact calving aims to maximise spring pasture and cow days in milk, before pasture quality and quantity declines in summer. Each extra cow day in milk before mid-summer is equivalent to an extra 1.5 kg of milk solids. This focus on increased milk solids output is at odds with the need to spread production throughout the year, so a compromise between these philosophies is necessary.

A tight calving pattern has been shown to be a common factor in successful farming systems in general (Burke 1999). Major threats to achieving this are cows which have prolonged periods of anestrum, late calving cows and poor estrus detection.

These potential problems, and by definition, the requirement for a tight calving pattern required to make use of this potential gain, relies on controlled breeding with an effective controlled drug release programme.

2.3.3 Increased Scale of Operation

To counter the increased size and globalisation advantage of overseas companies, the decision to merge two of New Zealand's two largest dairy companies has recently been completed. Over the last 80 years, the number of processing companies has fallen from over 400 to just seven. Although three companies were responsible for 94% of production until recently, now New Zealand Dairy Group and Kiwi Dairies, along with the marketing resources of the New Zealand Dairy Board have merged to form a globally oriented dairy company named Fonterra. Fonterra is the world's 9th biggest dairy processing company. Attaining this scale of economies should lead to unit cost savings and the ability to compete more effectively in the global marketplace.

Other advantages are increased marketing spending, and customer priority. According to the Boston Consulting Group, this restructuring is predicted to form a giant vertically integrated dairy organisation capable of lifting dairy earnings by NZ$300 million annually (Promar International 2001).

 Fonterra accounts for 7% of New Zealand's GDP. Although significant by New

Zealand standards, Fonterra is only a mid-sized player in a global market where scale is increasingly important. US production is predicted to gradually shift towards the larger and more cost efficient units in the West and Southwest of the United States. Such a shift is also likely in Europe and Canada. These huge companies are substantially bigger than Fonterra and may prove more efficient due to larger economies of scale.

However, with the right structure linked to the industry's new strategic plan, projections are that in 10 years the New Zealand industry will be earning around five times present levels, or, NZ$40 billion. To attain, and maintain, the higher herd sizes envisioned by an expanding dairy production base requires a dedication to advanced breeding technology. There is a fixed supply of skilled labour in New Zealand that is only just keeping pace with current demand.

Developments in automated breeding technology will have to maintain pace if they are to enable those few with the specialised knowledge to administer the technology to more and more animals. Artificial insemination technicians are already in short supply. Some travel to different parts of the country, thereby lengthening the season over which they apply their skills. Others are required to work double shifts at peak times. Automated controlled drug release products will help artificial breeding technology become less labour intensive.

2.3.4 Attaining Increased Per Cow Efficiencies

The trend is toward larger herds using less skilled labour. These production units do not the same level of contact between cows and people. The contact time between cow and human being can be as little as five seconds a day. That is not enough time to adequately monitor the general health of the animal, let alone work out if a cow is in heat. This is especially true of young cows in which estrus generally lasts for around seven hours (Mcara 2000, 21/11/2000 Evening Edition). This shows a need for a combination of advanced, automated estrus monitoring and control programmes and products.

2.3.5 Improving Reproduction Performance

Managing the estrous cycle more effectively can enable improved milk production with more calves on the ground earlier, lower breeding costs, fewer reproductive culls, and fewer inductions. All this while recognising that the welfare of animals and the environmental sustainability of agriculture is a top priority.

A successful mating programme enables a desirable calving pattern. Farmers have less control over conception rates during an artificial breeding programme but these can still be enhanced by increasing the proportion of cows cycling before mating starts, ensuring cows are correctly submitted for insemination. High producing lactating dairy cows exhibit a high rate of non-cycling and early embryonic loss (Nebel et al. 1997, 80:179). The mating programme must therefore actively plan to address these issues.

As mentioned, the New Zealand dairy production system is a comparatively low-cost, efficient system. This is because it works with the seasons to directly capture the pasture grown to produce milk. This system necessitates a 365 day calving interval with a condensed pattern of calving beginning in late winter so that utilisation of the spring pasture flush is maximised. Reproductive performance determines the sustainability of this system from one year to the next. The recent industry trends of increasing stocking rates, improving genetic merit and lactation lengths with an emphasis on production per hectare, are demanding more advanced breeding technologies to maintain a fertile herd in a sustainable system.

Essential aspects of any programme aiming to improve breeding efficiency are an in-depth understanding of the estrous cycle, and the relevant pharmaceutical science (Ogle 2000). As we find out more about how the complex workings of the naturally occurring estrous cycle functions, controlled drug delivery methods can be designed to take advantage of this new knowledge to increase fertility, shorten the time to calve, and improve quality, safety and efficiency of the drug regimen.

2.3.6 The Role of Estrous Control in Attaining Increased Dairy Efficiency

The central theme is that New Zealand must strive for increased efficiencies if it is to continue to be successful, and that better estrous control has an important part to play in many applications aimed at increasing efficiency at all levels.

Controlled drug release has traditionally been central to estrus control programmes, and as these programmes develop, they become more complex. Drug delivery technology must keep pace, being developed in conjunction with these programmes, to provide new and appropriate solutions in a timely manner.

2.3.7 Market Demand for Improved Estrus Products

New Zealand farmers have recognised this need for improved estrous oriented products. They operate with low capital investment in equipment, meaning that any expenditure on new systems is rarely considered. Accordingly, adoption rate of new technology is low due to the expense involved, even when it is perceived that it would be beneficial. Due to the marked decline in profitability during the 1990's, farmers have been slow to maintain and upgrade even the essential items of their capital equipment.

In spite of this situation, there is a real market demand for low cost, on farm pregnancy testing and heat detection systems. Improved estrus detection and control products are near the top of the wish list that farmers would be willing to pay extra for. Farmers are willing to pay around NZ$500 per set of cups or between NZ$20 to NZ$50 per cow (MRL Research Group 1997).

These market demands, along with the recent increase in payouts to farmers, provide impetus for research and product development in this area.

2.4 Estrous Control

Reasons for wanting to control the estrous cycle in cattle have been discussed above in the context of the wider dairy industry, and are also well documented by others (Rathbone et al. 2000, 1:201-228). It is now timely to list the more specific applications in one place before looking at the estrous cycle and how to control it with controlled drug release for maximum production efficiency.

Specific reasons for estrous control are:

- Reduce time and labour involved in estrus detection.
- Allow the use of set-time insemination where all selected females to be inseminated (naturally or artificially) are processed at once. This is more cost effective.
- Synchronise donor and recipient in embryo transfer programmes.
- Encourage non-cycling cows to start cycling.
- Enhance estrus behaviour in cows which exhibit silent heat for the purpose of easier heat detection.
- Make artificial insemination more practical. AI is best carried out herd wide simultaneously and its wider use promotes less risk of transmitting diseases.
- To time calving patterns closer to the desired optimum schedule.

2.4.1 Estrous Cycle in Cows

The purpose of the following discussion is to establish a familiarity with a useful and immediate application of drug delivery in farm animals, rather than being an authoritative and complete reference on the latest in estrous management. For the sake of brevity, it makes various simplifications and generalisations about the

complex nature of the estrous cycle. A more comprehensive description on estrous control and veterinary drug delivery can be found in the book *Controlled Release Veterinary Drug Delivery* (Rathbone and Gurny 2000, 1).

While not the main topic of this thesis, a basic understanding of the cow reproductive organs and endocrine system is essential before designing a drug delivery system to interact with it.

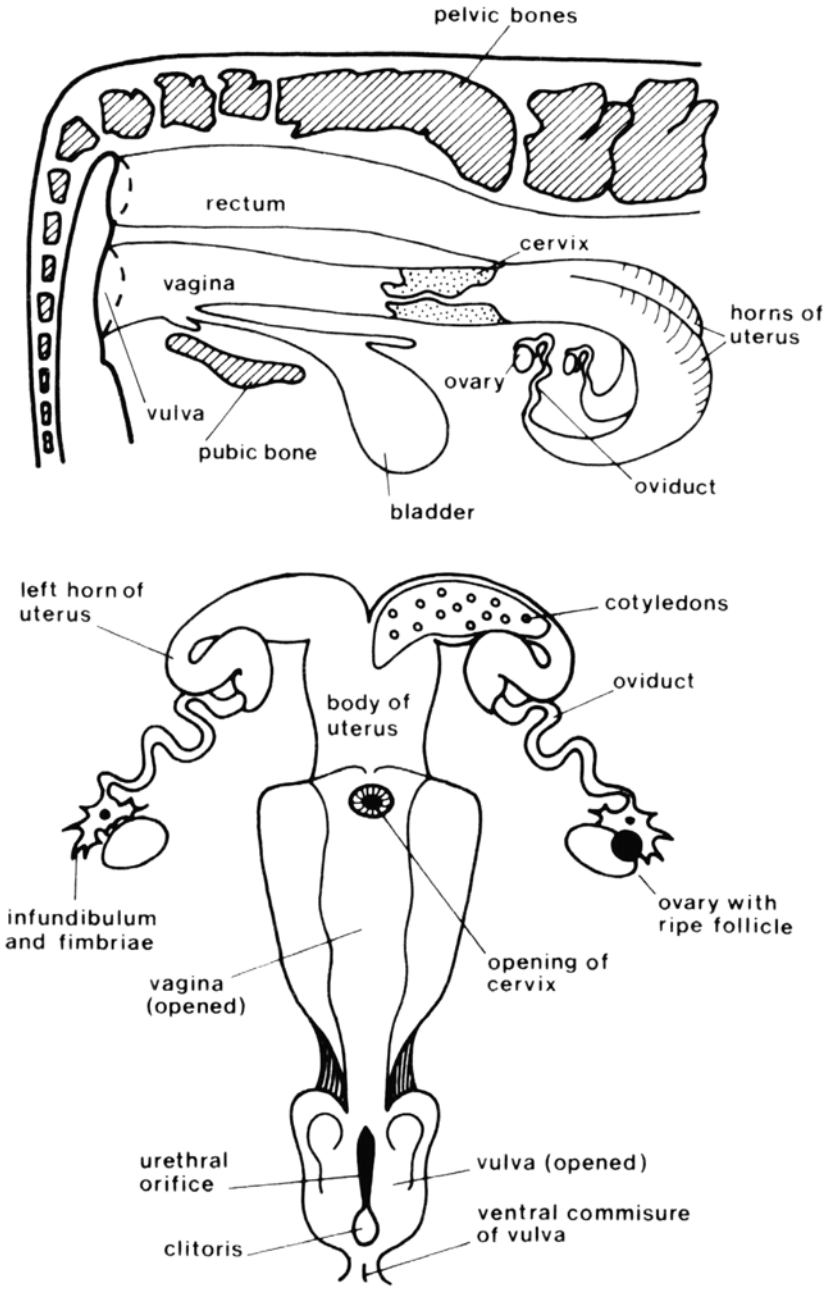


Figure 1: Anatomy of the Cow
(Webster 1993, 2)

Estrus

Occurring over a period of between 18 to 24 days (21 days on average, numbered 0 through 20), the cycle starts with the release of follicle stimulating hormone from the pituitary gland at the base of the brain. This triggers follicle growth in the ovaries over the next 12 to 36 hours (14 hours on average). Waves of follicular development occur throughout the cycle following pulses of lutenising hormone, which is required to make them active. After two or three such waves, a single follicle becomes dominant and ovulates. Ovulation occurs after the end of standing heat and is defined as day zero in the cycle.

The duration of heat can range from 2-30 hours with an average of 15 hours. This means that the state of ovulation can be predicted with reasonable accurately once estrus is detected. This allows Artificial Insemination (AI) or natural insemination to proceed with the most probability of success shortly after this time. A delay of several hours is recommended for AI since it is usually delivered directly into the uterus, in contrast to naturally deposited semen, which must transit the cervix.

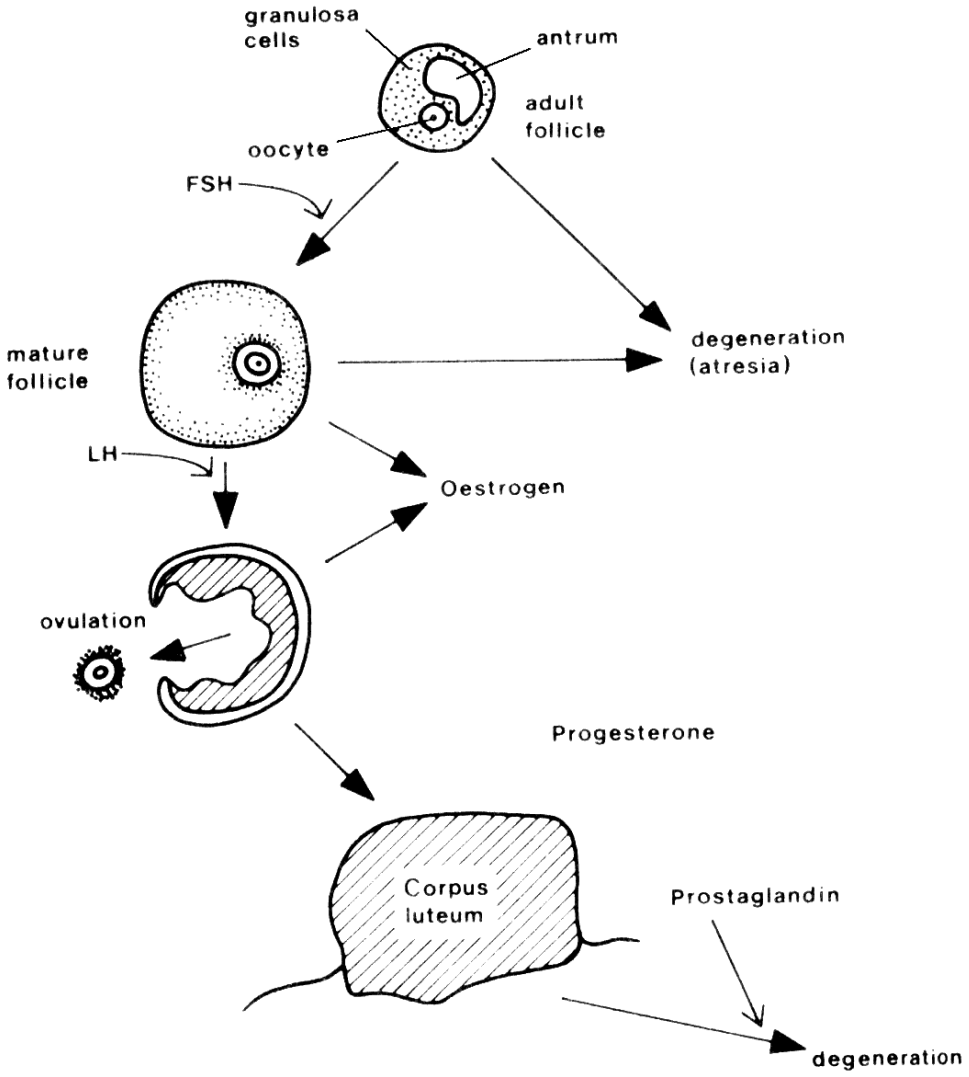


Figure 2: Cow Reproductive Process: Follicle Development and Degeneration
(Webster 1993, 2)

After Ovulation

Once an egg is released from the dominant follicle at the time of ovulation, the remaining part of the follicle then develops into the Corpus Luteum (CL). The CL releases progesterone for the rest of the cycle, which readies the uterus for implantation of a fertilised egg. Progesterone is the green light for the start and continuation of pregnancy.

If there is no fertilisation, prostaglandin $F_{2\alpha}$ released by the uterus acts to regress

the CL, resulting in a rapid decline in progesterone level. An injection of prostaglandin $F_{2\alpha}$ can likewise regress the CL. This lowers progesterone quickly and shortens the estrus cycle. However, the CL can only be regressed by prostaglandin $F_{2\alpha}$ if it is more than 6 days old (i.e. later than day 5 in the cycle).

If fertilisation does occur, the egg continues down the horns of the uterus and embeds in the uterus to develop. The subsequent release of interferon τ inhibits the release of Prostaglandin $F_{2\alpha}$ there by maintaining the CL and inhibiting further ovulation. Since the CL survives for the duration of the pregnancy, progesterone levels remain elevated.

Estrus Synchronisation by Application of Artificial Hormones

- Progesterone

A nylon insert coated with progesterone loaded silicone is used for controlled release. It acts like an artificial CL by releasing amounts of progesterone similar to normal physiological levels. This delays estrus to allow herd estrus synchrony and/or encourages non-cycling cows to commence the estrous cycle.

- Estradiol

Estradiol by injection performs two functions in a synchrony program; first to induce follicular atrasia at the commencement of a synchrony program and secondly to initiate estrus upon the withdrawal of progesterone controlled release devices.

- Prostaglandin $F_{2\alpha}$

One method for synchronisation is to give two doses of Prostaglandin $F_{2\alpha}$ by intra muscular injection 11 days apart. If the CL is less than 6 days old when the first dose is administered, there will be no effect, and the subsequent second dose will be certain to regress the CL. If the CL is more than 6 days old, both the first and subsequent second dose will regress the CL. In this scheme, AI is undertaken following the second dose of Prostaglandin $F_{2\alpha}$.

Prostaglandin $F_{2\alpha}$ may also be used as part of a synchrony program with other agents such as estradiol and progesterone. The role of prostaglandin $F_{2\alpha}$ in conjunction with other agents is to regress the CL should one be present. To achieve this with a single dose of prostaglandin $F_{2\alpha}$ it is administered towards or at the end of the synchrony program to ensure that any CL present will be greater than 6 days old.

2.4.2 Estrus Detection

Before the estrous cycle can be controlled, it must be detected and predicted with some accuracy. While, estrus detection may not seem immediately important in the process of drug delivery per se, the theme of this thesis is the automated control and monitoring of drug delivery for estrous control. In doing so, there is an emphasis on automated control of the delivery profile, based on the current state of the estrous cycle. It is necessary, therefore, to investigate what estrus detection methods are available.

The Cost of Missed Detection

There has been much research into estrus detection. This is because the cost of missed estrus to the farmer and the industry is high. The single most important factor contributing to reproductive failure in dairy herds is poor heat detection. Higher levels of milk yield per cow and fewer man-hours per cow (increasing herd size) have complicated this important chore and reduced the efficiency and accuracy of heat detection (Nebel and Walker 1998).

Expression of estrus behaviour is poor in lactating dairy cows compared to heifers (Nebel, Jobst, Dransfield, Pansolfi, and Bailey 1997, 80:179). Also, lactating dairy cows exhibit a high rate of early embryonic loss so it is important to pick up post AI estrus as an indicator of failed pregnancy. These two factors make it extremely important that estrus detection is effective on dairy farms.

Calving intervals longer than 12.5 months cost U.S. and Canadian dairy producers more than a trillion US dollars per year. Reproduction problems are the number one reason for culling on many dairy operations. In fact, more cows are culled for

reproductive reasons than for milk production reasons (Bou-Matic 2001). Reproductive experts calculate that it costs approximately three dollars per day for each cow in the herd that is open over 100 days. In the USA, once milking losses, replacement cost, calf losses, veterinary services, medication and added breeding cost is taken into account, the total annual cost per cow of estrous mismanagement there is US$89 (Bou-Matic 2001).

Figures for New Zealand farms are NZ$125 in lost production per missed estrus and a further NZ$110 per induction if subsequently required (Dexcel Ltd. 2001c).

Effective reproductive management means calving at an optimal interval. This synchronises lactation to peak levels of efficiency. When using artificial insemination, this relies on achieving effective detection of estrus.

Observable Signs of Estrus

The best behavioural indicator of estrus is standing to be mounted by another cow — so called *standing heat*. This mounting activity occurs on average 11 times per heat period with each mount lasting 3 seconds (Walker, Nebel, and McGilliard 1996, 79:1555-1561).

A summary of mounting behaviour and other effects is as follows (Dexcel Ltd. 2001b):

- Nervous, excitable, and restless.
- More likely to ride other cows and be ridden.
- May stand with back arched and tail in air.
- Spend less time than usual grazing.
- Display moist, red vulva.
- Clear mucus discharge from vulva.
- May hold milk.

- Frequently change from their usual order coming into the shed, often leading or lagging.

Visually detecting all standing heats is next to impossible though, because standing behaviour represents less than 1% of the total heat period. This fact has promoted the development of systems to detect this mounting behaviour which then bring it to the attention of the farmer.

There are two complicating factors that can make this difficult. One is the fact that *silent heat* is common among high producing dairy cows (Shipka 2000, 66:153-159). The term silent heat refers to the condition where the cow ovulates, but displays much a reduced observable behaviour.

The other difficulty is that many of the easily detectable signs of estrus are effects, rather than causes. For example, a slight increase in body temperature is one effect of estrus, but this can also be caused by an increase in ambient temperature, or the onset of illness (Fordham, McCarthy, and Rowlinson 1987, 11:367-379). Ideally, we want to detect causative factors for greater accuracy.

Methods of Estrus Detection

Commercially available heat detection aids for on farm use are based around the detection of behavioural signs in a manual or semi-automated fashion. As herd size increases and labour becomes more expensive there will be a greater adoption of some of these technological aids (Diskin and Sreenan 2000, 40:481-491).

Manual and automated methods for estrus detection (both experimental and commercially available) are listed below:

- Manual Observation

Estrus-detector animals (vasectomized or surgically altered bulls, or androgenized females) are allowed to roam among the herd. Social grouping, mounting and other behaviour is entered on a recording of observations and estrus expectancy chart.

Tail paint is the most common aid to the process of manual observation. The

water-soluble, latex based paint is rubbed off when another cow mounts, allowing the inference of mounting behaviour in the absence of direct observation. Correct use of tail painting identifies almost 90% of cows on heat (Dexcel Ltd. 2001c).

Tail painting also picks up cows that are only on heat for a short time and that might otherwise be missed, i.e. between milkings or overnight.

Kamar® is a similar product: Patches are glued to the coccygeal vertebrae of the tail head. Red dye is released after a specified time and pressure of mounting. Another variation is Bovine Beacon; a light stick that emits light for 18 to 24 hours or more after the stick is broken by mounting pressure. Although primary and secondary indicators of behavioural estrus are the best methods for determining timing of AI, breeding to an activated Kamar® device can yield acceptable results (Nebel et al. 1994, 77:3185).

There is little evidence for more frequent occurrence of estrus activity during nocturnal periods. The most marked decrease in mounting and total sexual activities occur at milking and feeding times. In spite of this, proficient dairy farmers using manual observation with tail paint should be able to adequately detect estrus in non-silent cycling cows, even if they can't be physically present around the clock (Pennington, Albright, and Callahan 1986, 69:2925-2934). The limiting factor for the manual observer is the degree of skill required and the time available to observe. If one or both of these are missing, automated forms of estrus detection will prove more cost effective.

- Ultrasound

Active follicles can be detected by ultrasound. Previously, these systems were difficult to use routinely in the field, but now self-contained head-mounted units are available. These are very effective but are used mainly by specialists due to the expense and level of training required.

- Palpitation

Palpitation via the rectum is a routine method for veterinarians to check the state of estrus by tactile detection of an active follicle. This is recommended practice

during the AI procedure.

- Electronic Pressure Switches

The HeatWatch® system from DDx Inc. consists of small, spread spectrum radio transmitters operating in the 900MHz band. These are placed inside disposable patches and glued onto the tailheads of cows. As mounting activity occurs, a radio receiver collects and transmits this information to a remote computer. The data can be collected and rebroadcast by repeaters to increase the range to a few hundred metres. The software on the computer at the end of the data link presents accumulated data on mounting activity. The manufacturers of HeatWatch claim a 95% detection rate (DDx Inc. 2001).

Also from DDx Inc., MountCount™ is essentially a simpler version of HeatWatch®, but instead of transmitting the information, it displays mounting status through three lights located on the device itself.

One disadvantage of these systems is that, being pressure activated, they will falsely trigger if the cow lies against a fence or similar object. Despite this, HeatWatch® has been used in number of estrus studies and has been found to be useful as a research tool, and as an on-farm estrus detector (Nebel and Walker 1998;Shipka 2000, 66:153-159;Walker, Nebel, and McGilliard 1996, 79:1555-1561).

- Motion Sensing

As explained, cows coming into heat will stand to be ridden, ride other cows and generally be more active. One study reported that cows in heat typically walk 2 to 5 times more than when they are not in heat (Nebel and Walker 1998). Another experiment concluded that peaks of physical activity coincided with estrus in 75% of the cases (Lewis and Newman 1984, 67:146-152). Nevertheless, motion sensing does not detect cows exhibiting silent heat as they display very little increase in activity.

The simplistic form of motion sensing uses a collar or leg mounted pedometer, typically incorporating a mercury tilt-switch to measure activity. Step counting

by a leg mounted pedometer is quoted as being 15% more accurate than collar mounted pedometers.

The Westfalia pedometer transmits both the stored activity information and the cow's identification each time the cow enters the milking parlour. The parlour computer then calculates an average activity level for the previous 10 days. If the value for that day is greater than 70% of the average, an estrus prediction is output.

Afikim produces the Afitag pedometer which is a similar device, while CowTrakker™ from Bou-Matic is a combination passive ID and motion sensing estrus detector mounted on a collar. The more sophisticated of these products use single or multi-axis accelerometer MEMS devices.

Overall, pedometery systems are moderately successful, with up to 70% of estrual periods, and 99% of nonestrual periods being predicted, depending on the exact type of system and the conditions in which the animals live (Koelsch, Aneshansley, and Butler 1994, 58). Barn housed animals are easily heat-detected because of the great peak in activity during estrus compared to the rest of their relatively sedentary lifestyle. In pasturally based systems, there is a higher level of background activity. Heat detection is still possible, but requires some post-processing of the data and there is a residual higher false positive indication.

- Body Temperature

Because temperature is such an obvious and easy variable to measure, it is no surprise to find that remote telemetry of vaginal temperature in cows has been done many time previously (Kyle, Kennedy, and Small 1998, 49:1437-1449;Redden et al. 1993, 76:713-721). Other studies of vaginal temperature in cows have been reported (de Mol 2001, 126:99-103;Gil, Szarek, and Kural 1997, 65:25-29;Kyle, Kennedy, and Small 1998, 49:1437-1449;Redden, Kennedy, Ingalls, and Gilson 1993, 76:713-721). Core temperature range is 37.8°C to 40.0°C, but usually does not stray far from 38.6°C during most of the cycle (Webster 1993, 2) given a moderate climate.

Temperature increases nearly a whole degree Celsius 12 hours before ovulation and drops back half a degree at the time of ovulation (Bobowiec, Studzinski, and Babiarz 1990, 44:573-579).

It has been suggested in unpublished (Verkerk 2002) work that the increase in temperature is due to the increased physical activity associated with normal heat and that the drop is attributable to ovulation.

For cows exhibiting silent heat, ovulation occurs without bulling or coming on heat. Since the increase in temperature is not present, it is interesting to speculate whether the drop in temperate due to ovulation might be used to indicate silent heat instead.

The answer is probably no, since even with a highly accurate thermometer, the small temperature change of less than one degree would be masked by other factors which also cause fluctuation in body temperature. These other factors include circadian rhythm, ambient temperature and the health status of the animal.

Even if the slight variation could be used to pinpoint ovulation it would be of little use. At this late stage there would be too little time to arrange for artificial insemination to coincide with the viable egg.

Remote monitoring of vaginal temperature in cows via a radio link has been accomplished more than one once (Kyle, Kennedy, and Small 1998, 49:1437-1449;Redden, Kennedy, Ingalls, and Gilson 1993, 76:713-721), and has also been applied to humans (McCreesh and Evans 1994:904-905).

Remote temperature sensing via radio from other parts of the body has also been accomplished many times, e.g. in poultry (Kettlewell, Mitchell, and Meeks 1997, 17:161-175), primates (Bergen, Tapp, and Reisman 1997:125-126) and cows (Lefcourt et al. 1993, 54:798-804;Lefcourt and Adams 1998, 76:1830-1837)

Methods utilising temperature to improve detection of estrus in dairy cows have been without wide acceptance of any one method. Kyle et al. (1998) found that the prediction of estrus based on vaginal temperature was excellent when an estral peak in vaginal temperature was defined as an increase of at least 0.4 °C for 3 or

more consecutive hours (detection sensitivity of 89.4% and prediction power positive of 85.7%). Corresponding detection sensitivity and prediction power positive for visual observations of standing estrus were 53.2% and 96.2%, respectively. The mean maximal increase in vaginal temperature at estrus was 0.9 ± 0.3 °C.

Redden, Kennedy et al. (1993) found that vaginal temperature increased by 0.6 ±0.3 degree C at estrus and remained elevated by at least 0.3 °C for 6.8 ± 4.6 hours. When increased vaginal temperature was used on an individual basis, 17 of 21 estruses were detected with 3 false positives.

Although these results look promising by themselves, temperature cannot be taken by itself as a reliable estrus indictor in isolation. Body temperature is also affected by circadian rhythm, ambient temperature and the health of the animal (de Mol 2001, 126:99-103;Lefcourt and Adams 1998, 76:1830-1837). Acute mastitis, for example, also increases body temperature. To complicate matters, these effects have a different influence dependant on the site chosen to be monitored (Fordham, McCarthy, and Rowlinson 1987, 11:367-379). No commercial products exist that exploit temperature by itself for sensing for estrus.

Surprisingly, vaginal temperature rise is not a good estrus indicator for other common farm animals such as pigs (Soede et al. 1997, 47:245-252).

- Milk Temperature

Prediction using temperature of the milk sampled from cows using an on-line sensor has met with a degree of success, being closely correlated with body temperature (Fordham, McCarthy, and Rowlinson 1987, 11:367-379;Gil, Szarek, and Kural 1997, 65:25-29). False positives from udders infected with mastitis can partly be eliminated by comparing the temperature from all four quarters. Infection, and therefore temperature rise due to mastitis, generally occurs on a quarter by quarter basis.

- Electrical Properties of Milk

As with on-line temperature sensing of milk taken from a milking machine, on-

line milk conductivity measuring has also been able to predict estrus with limited success (de Mol 2001, 126:99-103). Unfortunately, it suffers from the same disadvantage, being correlated with mastitis (Nielen et al. 1995, 78:1050-1061;Woolford, Williamson, and Henderson 1998, 65:187-198).

- Electrical Properties of Vaginal Mucus

Studies have shown that the occurrence of estrus is accompanied by an increase in electrical conductivity of mucus in the anterior part of the vagina, peaking after temperature (Bobowiec, Studzinski, and Babiarz 1990, 44:573-579;Gartland et al. 1976, 59:982-985). Conductivity starts at around 7.6mS and approaches 12.0mS before dropping again to 10.0 mS at ovulation. This conductivity fluctuation corresponds with the average temperate change, but lags by around 12 hours, and also has a reasonable correlation with milk progesterone. Variability is large between cows, however, indicating that a single measurement of electrical resistance is unreliable in distinguishing physiological states (Gartland, Schiavo, Hall, Foote, and Scott 1976, 59:982-985).

Electrical resistance of vaginal mucus on the cervix can be when the correct procedure is used. However, the procedure is time consuming and involves some skill. It must be positioned expertly in order to obtain reliable results (Wehner et al. 1996, Staff Paper SP 96-004).

- Hormone Levels

The role of progesterone was described in the section explaining the estrous cycle. Progesterone in milk or blood will provide excellent data on estrus status because it is a controlling variable rather than an effect. Progesterone levels in milk and blood are often used as a "gold standard" in accurately assessing the state of the estrous cycle, and particularly for identifying cows with silent heat.

Currently, the milk or blood sample has to be sent to a laboratory for analysis, but low cost on-line milk sensing products are being developed and are expected to

become available for every day use at each milking within two years[1].

Other hormones in blood can also be monitored for determining how the estrus cycle works and at what state it is in. For example, lutenising hormone peaks regularly during the follicle wave phase, spiking markedly around day 18 of the cycle.

- Multi-Variate

As stated, conductivity, temperature and other effects are influenced by more than one cause, so any system based on these factors alone will be ineffective. One answer is to use a combined analysis of a variety of measurable quantities can form the basis of a reliable detection system (Mitchell, Smith, and Sherlock 1995:-42).

Such a multi-variate approach using activity, concentrate intake, milk yield, temperature and conductivity has met with some success, but always with a variable number of false positives and negatives (de Mol 2001, 126:99-103;de Mol and Ouweltjes 2001, 49:71-82;de Mol and Woldt 2001, 84:400-410). In one trial, sophisticated filtering of an accumulated database with two years worth of data, true positives and true negatives for estrus and subclinical mastitis ranged from 65% to 99.4% (de Mol et al. 1997, 48:219-227).

- Other Experimental Techniques

Other, less obvious estrus detection techniques could also prove useful. These novel ideas in the experimental stage include breath ketone, urine and pheromonal analysis.

Applicability of On-line Milk Sensing Methods

In future, more efficient estrus detection methods for dairy cows might be based on on-line sensing of milk. Since this biological fluid is already being collected

[1] The author is an employee of Sensortec, who specialise in developing such on-line sensors. Sensortec's relationship to this thesis is described in the preface.

from the animal on a daily basis, it would be convenient to sample it for estrus detection. Highly specific and sensitive tests are being developed to reduce the response time and cost of these systems to measure pregnancy and other factors in milk (Ellison 2001, Publication No. 211:41-45). Progesterone levels remain elevated during pregnancy but should cycle if the cow is not pregnant. False positives for pregnancy occur frequently, but the important condition of not being in calf (low progesterone) is always picked up (Webster 1993, 2).

The focus of this thesis is on a drug delivery device mounted in or on the animal, so on-line sensing is not appropriate to discuss at length. However, milking robots which have the capability of measuring milk temperature and conductivity from each quarter could be used to transmit activation signals to an on-cow drug delivery device.

Future Trends in Estrus Detection

For the commercial farmer, the manual collection of data for analysis is more effort than it's worth. In addition, the more accurate and sophisticated tests based on hormonal changes (i.e. causes) can only be carried out in the laboratory. This means that this type of data for each individual cow is done only once or twice a year (herd testing). Somatic cell count and other factors are measured at each milking, but only for the herd as a whole from a bulk tank sample.

To address these issues, and improve the quality of life for dairy farmers, robot milking systems have been developed. In these systems, the cows attend a robotic arm which places the cups on the cows teats automatically. There are a few hundred of these systems operating worldwide, mostly in Europe.

Some robots also carry out a range of other cow management activities. The Merlin robotic milking system from Fullwood Fusion cleans, milks and feeds the cows on an individual basis. It also measures, stores and displays data useful for estrus detection[2] through the use of sophisticated herd management software

[2] Sensortec has a conductivity sensor for Merlin in the final stages of pre-production. Somatic cell counting, blood contamination and fat measuring devices are also being developed.

(Fullwood Ltd. 2001b;Fullwood Ltd. 2001a). Currently, the machine makes predictions of certain events such as lameness and estrus. Such a cow will find itself drafted to a separate holding pen for the farmer's attention.

Strongly abnormal results trigger the machine to carry out immediate actions by itself. For example milk containing blood would be diverted from the bulk tank.

This is part of a continuing trend which will see more accurate physiological based testing carried out routinely at each milking and for each cow. The accumulated results will be stored by sophisticated database software for greatly enhanced herd management and automated response activities.

2.4.3 The Role Of Machine Readable ID Tags in Estrus Detection

Definition

There are many ways of uniquely identifying animals. The printed or laser etched ear tag provides a human readable number which is easily discernable. Laser printing is more durable.

Occasionally, the ear tag gets caught on something and is accidentally ripped out. If tagging is especially important, the tag may be applied to both ears. Incorporation of a bar code promotes automating identification, but this still requires the presence of a human to position the scanning device.

Radio Frequency IDentification (RFID) lends itself to a more automated approach. RFID works on the exchange of information between a reader and the tag using electric fields, magnetic fields, or both. More sophisticated versions include the ability to store information on the tag for later retrieval. The tag itself may exist in the form of an ear tag, be mounted on a collar, or strapped to the cow's leg. A tag in an injectable glass pellet form is widely used to uniquely identify pets.

Active tags have batteries that provide them with a read range of a few metres. Passive tags do not require batteries, but have a range of less than a metre. They

obtain their power from the coded interrogation pulse. Anti-theft labels in clothing and music stores use this technology.

Machine Readable ID Tags in Controlled Drug Release

Machine readable ID tagging is an essential part of many automated herd management functions. This tagging has many additional uses and it will become increasingly cost effective as the uses of ID tagging expand. For this reason, a machine readable tag should be included in any long term electronic drug delivery device, e.g. rumen implant. To prove this point, an inter-cow communication scheme using cow ID is added to the in vivo drug delivery device developed in later chapters.

In fact, animal identification is important in many applications ranging from pet security to salmon migratory studies. Many machine readable ID tag products exist for these markets. Automated estrus detection can also make great use of animal ID: the identity of the cow must be available with estrus information for it to be of any use.

Cost Effectiveness in Multiple Applications

The CowTrakker™ product, mentioned earlier, is a combination passive ID and motion sensing estrus detector mounted on a collar. It has been proven to detect when cows are in heat, or are unwell. The manufacturers of such devices state that they are cost effective, even considering their high per-cow initial cost of deployment (Bou-Matic 2001).

This is probably only true for overseas farm conditions due to the fact that the passive ID is included in the same package. If a passive ID tag is required on the animal, then including motion detection for little extra cost makes sense. In New Zealand however, machine readable ID tags are rarely used so the cost involved to use such a device purely for estrus detection does not compare with the cheap and effective tail-paint method (Burke 1999).

In future, European legislation is expected to make machine readable livestock ID tagging compulsory due to a desire for traceability. It is already technically

feasible to trace an animal from the moment of birth, through processing, to the checkout counter at the supermarket.

Organic produce authentication for the consumer is a prime example of the need for better traceability. The use of antibiotics and chemotherapeutics in animal husbandry has led to the occurrence of veterinary drug residues in all types of food of animal origin (Sternesjo, Mellgren, and Bjorck 1995, 10.1006:175-181). Organic produce is increasingly in demand, and since the consumer expects to pay a small premium, this allows for the extra costs involved. When this demand strengthens considerably there could be strong market pull for machine readable ID in European countries and countries that wish to export there.

Establishing cow ID automatically is also advantageous if sampling milk from individual cows, and compulsory when a robotic milker is used, since there are no humans there to make the identification. Once identified, on-line sensors, pedometery devices and other sources of information can predict for cows on heat, cows that are giving colostrum, or cows having health problems. The milk from these cows can then be routed to an alternative destination if required, and the individual feeding and drafting actions carried out automatically for each cow.

There are many examples of useful applications in which it is not economically feasible to apply machine readable tagging for that purpose alone. However, if used for a range of activities, the cost/benefit threshold can be met. Examples of these ancillary applications include being able to automatically prevent a mastitically identified cow from being accidentally milked in a conventional milking parlour. Even activating an audible alarm would be enough to save a complete bulk tank being ruined by milk contaminated with somatic cells or antibiotic treatment from an mastitic cow.

Food Safety

There are some issues with food safety for the consumer when any device is attached to an animal intended for human consumption. Although RFID tags in small beads injected under the skin are less prone to tampering, they can sometimes migrate of their own accord, making them difficult to remove during

meat processing. It is therefore a minimum requirement that they be safe to ingest if this happens by accident.

If tags become unpopular, other means of identification that lend themselves to an automated approach include nose print and iris identification. Iris identification looks more promising than nose printing because it is a non-contact method. It is an experimental technique which works by assessing the 500 or so measurable metrics from an automatically acquired image of the iris. Currently in commercial use for human eye recognition, a version for animals has been trialled. One disadvantage is that the iris pattern is not stable in cattle until 6 months of age.

2.5 Controlled Drug Release for Estrus Control

It has now been established what the estrous cycle is, why estrous control is important, how estrus may be detected, and the consequences if it is missed. This section describes the aims and methods of controlled drug release for estrous control along with experimental and commercially available products for doing so.

Depending on the needs of the farmer, the use of estrus control products may be restricted to just a few cows in every hundred. If the farmer is not concerned with synchronisation, but simply wishes to "jump start" non-cycling cows, then only 10% to 20% may require treatment.

2.5.1 Controlled Drug Release: A Definition

Traditionally, the easiest way to delivery a drug was to administer it in a high dose by pill or injection at a given time. Repeat doses followed when the initial effect started to wear off. This is inconvenient, uneconomic and sometimes results in damaging side effects. Controlled drug release aims to overcome these issues by giving drugs continually for prolonged time periods, in a controlled fashion, and to the preferred site (Rathbone and Gurny 2000, 1). The primary method of

accomplishing this has been through incorporating the chemicals within polymers.

The advantages of controlled release are stated as having the potential to:

- Use less drug.
- Be more effective.
- Have fewer side effects.
- Increase patient compliance (in humans).

One application for controlled drug release is to synchronise cattle for artificial insemination and reduce the time to breed. In designing such products, there are a number of factors to consider. These range from raw effectiveness through to animal welfare and economics. Influencing these factors is the ability of the underlying drug and delivery method to facilitate administration, provide adequate absorption and bioavailability, and to control the time and place of release.

2.5.2 Advantages of Electronically Controlled Drug Delivery

Electronically controlled drug release has the potential to ease delivery in a number of areas including chemotherapy, insulin delivery, pain management, antibiotic treatments and AIDS therapy. This is because electronic control provides various abilities not otherwise easily obtainable:

- The advantages of controlled release over uncontrolled release have just been described. The finer control provided by electronic means will enhance these existing benefits.
- Electronic control can enable an otherwise simple mechanism to exhibit an arbitrary delivery profile, rather than being restricted to the standard exponential decay or square root of time responses. To be sure, non-electronic alternatives can deviate from these classical delivery profiles: Varying the thickness of dissolvable coatings on beads is one way to accomplish this. However, these techniques are somewhat dependant on

the environment they operate in. They are often affected by changes in temperature and pH etc.

- In-built intelligence, coupled with electronic sensors make the device self-aware. These sensory inputs can affect program execution, the result of which can be used to alter the delivery profile. Delivery rate could be decreased proportionally with increase in temperature. An emergency response bolus could be activated if heart rate is out of normal limits.

- The existence of electronic circuitry can facilitate incorporation of additional electronic functions. Once an electronic system is present, there is relatively little effort in providing additional functions such as status indication, external control and telemetry. Temperature telemetry is very common in this respect since it is easy to include and is an important biological parameter.

2.5.3 Established and Experimental Routes of Controlled Drug Delivery

Subcutaneous and intravaginal routes have been used successfully in the control of the estrus cycle in cows and ewes on a commercial scale (Rathbone, Burns, Ogle, Bunt, and Burggraaf 2000, 1:201-228). For a drug to be useful via the intravaginal route, it must be have rapid absorption, a low minimum effective concentration, be relatively soluble and be non-irritant.

Alternative routes used for other experimental and/or commercial applications in animals include ocular (Gurny et al. 1997, 28:335-361;Li et al. 1986, 3:213-218;Olejnik et al. 1985, 37:118), ruminal (Rathbone and Gurny 2000, 1), oral (dental) (Cleland 2001, 50:261-275), rectal and intra-muscular (Mason et al. 1996, 13:243-252).

Transdermal patches and topical treatments for veterinary use have also been investigated experimentally. There are limitations with current transdermal technology developed for human use when applied to animals due to differences in body mass and skin transport properties (Riviere and Papich 2001, 50:175-

203). Topical treatments are currently in veterinary commercial use and more are being developed as it becomes clearer how drugs are transported across the skin barrier (Magnusson, Walters, and Roberts 2001, 50:205-227). Not all routes allow the transport and absorption of the chosen active biological material, so this restricts the route choice significantly. To address this issue, iontophoresis electroporation and sonophoresis techniques are being developed. These techniques are explained later on in this chapter, starting on page 41.

2.5.4 Commercial Products for Estrous Control

Commercial products are based around the three main types of programmes:

- Prostaglandins: e.g. Lutalyse®, Estrumate®, IN-SYNC®
- Progestins: e.g. Syncro-Mate-B®, Melengestrol Acetate, CIDR®, PRID®.
- Gonadotropins: e.g. Cystrolrelin®, Factrel®, Fertagyl®

Most programmes are designed to control the corpus luteum, while more recent products control ovulation, follicular development, or a combination of these. They work mainly by artificially controlling levels of hormones in the blood which act as messages to regulate the activity of the tissues involved in the reproductive cycle (Rasby and Deutcher 2001). Each product requires its own protocol and often involves the use of one or more injections at specific times.

Controlled release products include P+® which is an intramuscular injection of microspheres to control the estrous cycle in heifers. SYNCRO-MATE-B® and Crestar are silicone subcutaneous ear implants for cattle. CUE-MATE®, PRID® and CIDR® also contain loaded silicone, but are intra-vaginally located devices. The CIDR® is a T-shaped device with a nylon core, while the PRID® is similar in concept but has a stainless steel core in the shape of a spiral.

Silicone devices have the disadvantage of having to be monitored while in situ, and have to be removed. In the case of the intravaginal devices, this is a reasonably simple task. Intravaginal devices offer unique advantages and disadvantages, and are an under exploited delivery route in general (Rathbone et

al. 2000, 1:173-200).

The silicone subcutaneous implant technology, often located in the ear, requires a minor surgical procedure which leaves the animal open to possible infection. Implants can migrate under the skin and rogue implants are a possible source of rejection at the meat processing works when the cow is culled.

One alternative is a subcutaneous injection, fluid enough to be administered by syringe, but which hardens into an implant shortly afterwards. The implant dissolves in a biodegradable fashion over time. SABRE MATE® is one such product.

Current best practise to provide synchronisation is achieved by a seven or eight day delivery of progesterone from a slow releasing in-ear, or intravaginal device, followed by an injection of estradiol or prostaglandin to control follicular development. While it is impossible to describe here how all of the listed products work, two that follow this type of protocol are described more fully. It is useful to examine these in closer detail for the purpose of assessing what kind of drug delivery capability is required of the forthcoming experimental system.

CIDR®

The CIDR® device from InterAg[3] is a T-shaped intravaginal insert made of silicone with a nylon core. The silicone matrix outer is loaded with 1.38g of progesterone to prolong follicle development. Elution of the drug follows the standard square root of time curve over nine days. Manual injections of a estradiol benzoate (by the trade name of CIDIROL®) are then required as in Figure 3.

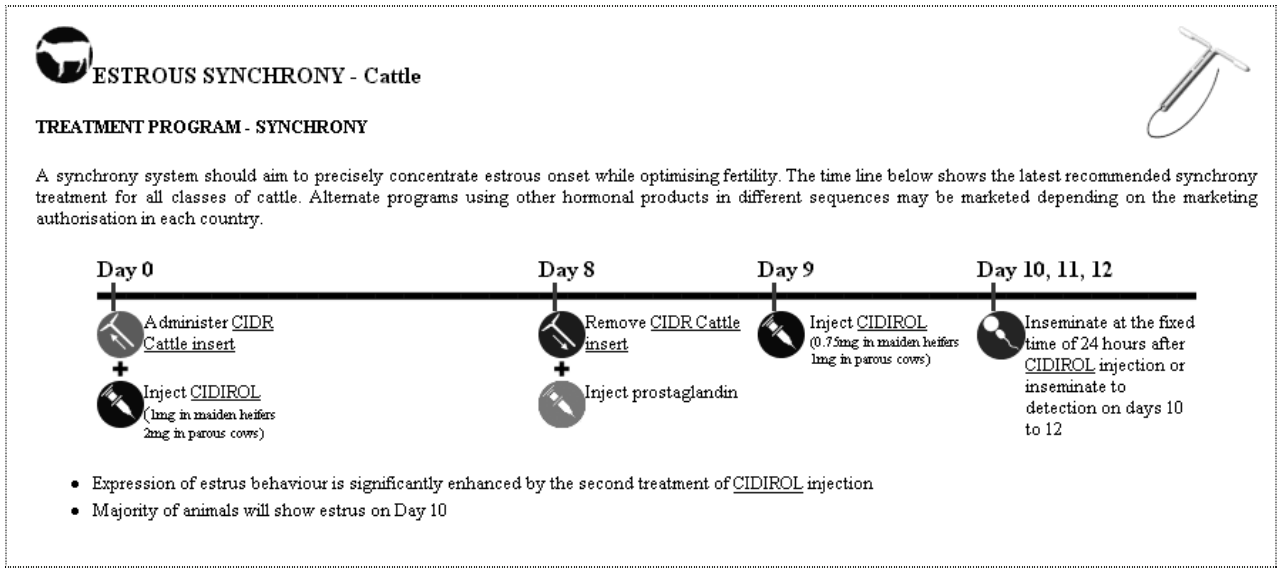

ESTROUS SYNCHRONY - Cattle
TREATMENT PROGRAM - SYNCHRONY
A synchrony system should aim to precisely concentrate estrous onset while optimising fertility. The time line below shows the latest recommended synchrony treatment for all classes of cattle. Alternate programs using other hormonal products in different sequences may be marketed depending on the marketing authorisation in each country.
Day 0
Administer CIDR Cattle insert
Inject CIDIROL (1mg in maiden heifers 2mg in parous cows)
Day 8
Remove CIDR Cattle insert
Inject prostaglandin
Day 9
Inject CIDIROL (0.75mg in maiden heifers 1mg in parous cows)
Day 10, 11, 12
Inseminate at the fixed time of 24 hours after CIDIROL injection or inseminate to detection on days 10 to 12
Expression of estrus behaviour is significantly enhanced by the second treatment of CIDIROL injection
Majority of animals will show estrus on Day 10

Figure 3: Application of CIDR® to Bovine Estrous Cycle
(InterAg 2000)

SMARTT1® Intelligent Breeding Device

The SMARTT1® Intelligent Breeding Device (IBD) from Plade Holdings has batteries and an electronic timing system to deliver one reservoir of 5mL of drug over an extended time period. A solenoid operates a valve that controls the drug under pressure from a spring pressurized piston. The drug is released in small bursts, several hours apart and timed to compensate for decreasing spring force as

[3] The relationship between InterAg and this thesis is stated in the preface.

the reservoir is depleted. In addition, there are three small spring loaded bolus pistons that are activated by melting a plastic thread over a resistor. This device attempts to deliver a drug programme comparable in nature to that used with the CIDR®, but in a more automated fashion. Later versions of the device have more sophisticated delivery regulation.

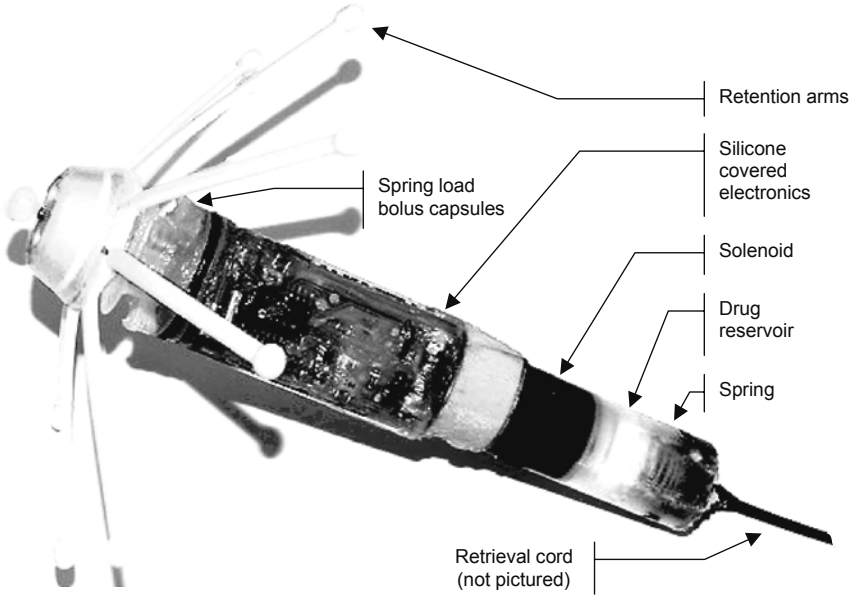


Figure 4: SMARTT1® Intelligent Breeding Device
(Plade Holdings 1999)

There is no doubt that the SMARTT1® IBD should perform well in the kind of physical drug delivery task it was designed to do. However, this method of delivery is not suited to development into a more complex device capable of high accuracy and adherence to a complex profile incorporating both high and low delivery rates.

There are two reasons for this: Due to the fact that so much room is taken up by the battery and electronics, there is little room left for the main reservoir. This means that the drug must be concentrated; any error in absolute volume leads to a higher error in dosage. Secondly, the nature of the spring loaded, controlled orifice release mechanism is such that any small blockage could adversely affect dosage after that point.

2.5.5 Selected Electronically Controlled and Actuated Variable Rate Drug Delivery Technologies

This discussion on devices and technologies is not specific to any animal or human application, nor to any route. Its purpose is to provide some background on previous experimental work on electronically controlled and actuated drug delivery before considering the design of the drug delivery platform used in this thesis. Due to space limitations it covers only a few selected technologies.

This short review concentrates only on technologies that involve electronics close to the *actuation* of the dosage form, whether it be by direct application of a voltage, or via an electrically stimulated transducer. It is conceivable that an electronic circuit could be added to any form of drug delivery mechanism. However, this review is more concerned with electronic actuation because it is likely that this approach would lead to smaller, simpler, more reliable devices.

Stimulated Polymer

Elution of the drug usually follows the standard square-root-of-time law. The existing knowledge and manufacturing experience using this technology can be extended to more complex delivery profiles by using electric or magnetic fields, exposure to ultrasound, light or enzymes, and changes in pH or temperature.

Microchip Array

A silicon based integrated circuit provides controlled release of single or multiple chemical substances on demand (Santini jr, Cima, and Langer 1998;Santini et al. 2000, 32:377-379;Santini, Langer, and Cima 1999, 397:335-338). Micro-reservoirs filled with chemicals in solid, liquid or gel form are covered by a cap consisting of a thin layer of gold film that also acts as an anode. An electrical voltage applied between the anode and a cathode causes a reaction that dissolves the cap, releasing the chemical. Controlled and pulsatile release of chemical substances with this device has been proven in the laboratory and a company called MicroCHIPS has been formed to commercially exploit the new technology.

 Potential advantages of this approach include small size, low power consumption,

absence of moving parts, and the ability to store and release multiple drugs or chemicals from a single device. The main disadvantage is the tiny amount of room available for drug storage which makes it impractical for doses over 10μL.

Micro Needle Array

Microneedles are microfabricated devices for minimally invasive drug delivery applications which can be integrated into a variety of devices (Zahn et al. 2001:503-506). A portable drug delivery device with integrated microneedles and on-chip MEMS positive displacement micropump has been developed (Santini jr, Cima, and Langer 1998;Santini, Richards, Scheidt, Cima, and Langer 2000, 32:377-379;Santini, Langer, and Cima 1999, 397:335-338). This works by generation and collapse of thermally generated bubbles which propels the liquid drug along the length of the needle, while check valves assure pumping in the desired direction. Very low rates of volume are possible: down to 1.0 nL/s.

Hydrogel

Researchers are developing a device made from porous hydrogel. Once inserted, it is capable of expanding to several times its own size. This device is about the size of a matchstick, and perforated with microscopic hydrogel controlled holes. The hydrogel is addressed by a backing of conductive plastic. Current flowing through the backing makes the holes in the hydrogel open, allowing it to release variable amounts of medication.

Iontophoresis

Ionic or non-ionic drugs can be persuaded to move by applying a voltage gradient. Drug flow is proportional to current flow, allowing a constant or varying delivery profile (Zhao, Hung, and Choy 1997, 23 Suppl 1:S27-S29).

The resistance of skin varies greatly. Sensation of current flow can be felt by most humans at around a threshold of 150μA/cm^2, however, skin can begin to be damaged at a level ten times lower than this. A direct current source has higher efficiency but has some side-effects. The pulsed direct current technique has little side-effects, but the efficiency is lower.

Examples of commercial iontophoresis drug delivery systems are the Phoresor from Iomed (Salt Lake City, USA) and the DUPEL from Empi (St. Paul, USA).

Electroporation

Also called electropermeabilisation, electroporation is when the cell membrane permeability (and electrical conductance) drops due an applied voltage (Berner and Dinh 1998).

When a short pulse is suddenly applied to the membrane, conductance is relatively low, allowing it to charge up as the electrical field is established. The current is then relatively stable for a short time period (on the order of one microsecond). Breakdown then occurs and the membrane becomes unstable. During this time, the membrane is permeable to substances it would otherwise present a barrier to. In some cases, the action causes permanent damage, but in most cells and tissues it is reversible if short pulses of about 10μs are applied in a square-wave type fashion.

Drugs can be loaded into cells in this way, allowing them to travel to the intended zone, transported and protected by the body's own mechanisms. Electroporation can also be used for gene transfer (Zhao 2000, 133:37-43).

Sonophoresis

Sonophoresis, or phonophersis, is the use of ultrasound to enhance delivery through the relatively impermeable skin barrier and down into the soft tissue where it can be absorbed (Berner and Dinh 1998).

Therapeutic action occurs in the ultrasonic near field which is effective at up to a 1cm depth at a frequency of 1MHz (further at higher frequencies). A contact medium is necessary due to the fact that there would otherwise be complete reflection from the transducer/air interface at such a high frequency.

While not sonophoresis per se, another experimental use for ultrasound is to stimulate a pellet embedded in the eye. This enables periodic ocular drug delivery without having to re-insert a foreign object into the eye with each dosage.

Implantable Infusion Pumps

These are often embedded under the skin to deliver drugs . Some devices can be refilled percutaneously. Applications include cancer chemotherapy and long term pain relief. Componentry generally consists of a battery, electronic controller, reservoir, and pump inside a biocompatible housing.

The pump mechanism itself may be a miniaturised peristaltic pump driven by a stepper motor, or a piezoelectric diaphragm pump. Both pump types have an inherent safe guard built-in: They only pump when a pulsed voltage of approximately the right frequency is applied. This acts as a mechanical check in case the electronic driver circuitry fails in one particular state, which is the most common failure mode.

There are many such commercial devices. Medtronic Inc. make the SynchroMed model which is percutaneously refillable and includes a programmer that can communicate and program the embedded device over an RF link.

Electrolytic Gas Powered Pumps

The general method of propelling a liquid vehicle from electrolytic gas production is well established. Many patents have been granted for variations on this method (Bae and Kwon 1993;Bae and Kwon 1994;Gross and Zucker 1993;Herres 1994;Winsel 1993;Wyssmann 1998).

Most of these mechanisms rely on a constant gas production to provide a relatively constant rate of drug delivery. In such a system, there is generally a battery to supply current, and a fixed resistor connected in series with the gas generating cell. The resistor primarily determines the current flow, and hence rate of delivery is constant. By selection of appropriate battery chemistry, the variation in voltage during discharge does not unduly affect delivery rate.

An extension of the constant gas production technique can provide pulsed delivery. This is achieved by making the drug reservoir a thin long tube. The drug in liquid form is present only in slugs distributed along the tube, separated by sections of air. As the gas production proceeds at a constant rate at the sealed end

of tube, the slugs are delivered periodically in a pulsatile fashion at the other end. Naturally, delivering air along with the drug limits the field of application. Nonetheless, a delivery device with a coiled tube for the pulsed release of nitroglycerine has been developed and demonstrated successfully for transdermal application (Groning and Kuhland 1999, 193:57-61)

To go beyond constant rate or simple, predetermined pulsed delivery, requires the addition of some control circuitry. Such devices allow complex drug delivery profiles to be designed before activation commences. Modification to that profile can occur during the programmed delivery based on external control or information from environmental sensors.

Practical devices along these lines have been built and assessed for reliability and accuracy of delivery. A rudimentary device of this type consists of a small tube, 25mm long, with batteries, a magnetically operated reed switch, a gas production cell and a drug reservoir (Groning and Weyel 1993, 39:102-104). A battery supply can be turned on and off by a reed switch external to the patient. A computer controls an electromagnet up to 10mm away, which in turn affects the reed switch, and ultimately the rate at which the drug is delivered. The control of this device was successfully demonstrated in the laboratory at varying rates.

Kim (1999) reports of a more sophisticated pump: an ambulatory infusion device developed to provide drug delivery at a precisely controlled rate. The pump module contains medication separated by a flexible membrane from a gas-generating chamber with an electrolytic cell. The control module alters the driving current level depending on the infusion rate required. A microprocessor calculates the current level required based on selected infusion rate, ambient pressure and ambient temperature. The accuracy and precision of the device was verified over varying environmental conditions and flow rate rates (0.1 to 100 mL/Hr). Flow rate was found to be accurate within ±5%.

Electrolytic gas powered pumps are easy to construct, have been proven to deliver complex profiles, and can cope with a large range of required flow rates.

3. Development of a Practical Drug Delivery, Communication and Monitoring System

3.1 Introduction

Drug delivery in farm animals for uses such as controlling the reproductive cycle in cows has centred on injections and/or silicone inserts which permit the slow release of a hormone over a number of days. In these commercial protocols, the reproductive cycle is usually monitored on a manual basis.

InterAg has experimented with an intravaginal constant rate drug delivery device with the aim of facilitating continuous delivery over a period of up to two weeks. This experimental system is based on a commercially available syringe, the piston of which is moved by production of hydrogen gas from a gascell. The value of a resistor determines the fixed rate of delivery. No battery is required since the act of drawing current from this special button cell produces the gas.

This is a type of electrolytic gas powered pump described in Chapter 2. There, it was stated that electrolytic gas powered pumps have proven to be easy to construct, easy to control, are accurate in delivery, and can cope with a large range of required flow rates.

Such a system would be greatly enhanced by the addition of some intelligence, memory and the ability to communicate with the outside world. This proposed system of drug delivery would then be capable of providing a more complex drug delivery profile. With two-way communication, recorded events such as temperature readings could be transferred to the outside world to allow for the condition monitoring of the animal. More importantly for the subject of this

thesis, external control of the device could be obtained.

Once this basic form of communication has been established, an automated drug delivery and results collection network could be developed. This system would integrate these individual inserts into a tool capable of drug delivery and monitoring where behaviour of the device could be changed autonomously, or externally via wireless control, as delivery progresses.

This chapter documents the development and bench testing of such a system. The following chapter describes its use in an experiment in vivo.

3.2 Contemporary Controlled Drug Release Design Philosophy

Historically, products have come about from "animal need". After an academic or market research study, a perceived animal need leads to a drug choice and then to a route and method of delivering it. But this approach is no longer good enough. Instead, a "technology" approach is required: Delivery platforms capable of being designed in advance of a particular use can provide a wider range of function and hence applicability (Rathbone 2000). As much as possible, they should be independent of:

- Delivery route (e.g. intra-vaginal, subcutaneous, ruminal).
- Drug type.
- Required activation period.
- Required range of flow rates.
- Animal to which drug delivery is applied.

Only the various parameter settings should need to be tailored to match the technology with the specific application.

Additional desirable attributes are:

- Biodegradable:
  - No effort required for removal.
  - No environmental impact due to discarded devices.
- Capable of delivering multiple drugs.
- Capable of delivering complex drug profiles including variable rate, stop/start and bolus.

While the attitude displayed in such a design philosophy is admirable, it is exceedingly difficult to implement from an engineering perspective. After initial implementation choices are made for the core technology, the main design decisions are usually centred around compromise in order to achieve adequate performance. Often, equally important design criteria contribute to opposing design goals. A device may need to be reduced in size to fit into a particular cavity, but the act of making it smaller decreases the accuracy of the intended delivery because the formula must then be more concentrated. Radically new technology is sometimes required to leapfrog over such limitations.

The philosophy above was noted in the course of developing the following system, but compromises were made in order to produce a device within timeframe and resource constraints. To limit the amount of risk involved, standard techniques and off the shelf components were used where possible. A critique of this design process is presented in the discussion section.

3.3 Requirements of the Proposed Drug Delivery System

Analysis of InterAg's requirements, their present experimental delivery device, and the literature review section of this thesis lead to a detailed specification of what was required in a full system. The need to demonstrate original results for this thesis was also a major consideration.

The system requirements are deemed to be:

- Able to be located in the cow vagina for up to two weeks:
  - Be sized and shaped for comfort and retention.
  - Must withstand the physical environment: Ingress of moisture, mechanical stresses, chemical attack from urine and faeces.
- Precise delivery of 40mL of pharmaceutical gel vehicle for controlled release:
  - Easily design a volume rate profile on a PC and download it to the device.
  - Short or extended periods of delivery time (from one day, up to three weeks).
  - Delivery in accordance with a complex profile with a continuous range of possible rates between 1 mL/day up to 40 mL/day (80mL/day peak).
  - Accuracy of 10% in real world conditions in vivo.
  - Safety limit overrides for temperature, pressure, motion and volume.
  - External control (start/stop override).

- Machine readable ID number.
- Human readable ID number.
- Interface with outside world via digital data wireless network:
  - Two way.
  - 30m range.
  - Transmit through any matter that might cling to the device.
  - Data rate sufficient to transfer a week's worth of data in five minutes.
  - Inter-cow communication.
- Environmental sensors for monitoring the animal and the device:
  - Temperature.
  - Pressure.
  - Motion.
  - Light.
  - Cow Proximity.
- Data logging:
  - All environmental data above.
  - Drug delivery progress.
  - Device self-diagnostics.
  - 15 minute resolution.
  - Sufficient capacity to hold a week's worth of results before result sets are overwritten, starting with the oldest record.

- Snap-shot of information available over wireless link. A manually initiated process to get the current status of the device rather than having to wait until the end of the data logging period.

3.4 Overview of DMU Operation

To satisfy these requirements, the Delivery and Monitor Unit (DMU) is designed as a vaginally insertable device that allows a variable rate drug delivery profile to be carried out. The profile is defined on a rate-of-volume versus time graph on a personal computer and is downloaded to the DMU before insertion. Sensors monitor the state of the device and its environment and can inform a rule-based intelligence to dynamically alter the rate of delivery.

The miniaturised electronics package occupies a volume of 16mL including batteries. It includes a two-way wireless data link for manual override, device interrogation and data log download. Data logging of 27 different variables occurs every 15 minutes for a two-week period.

Once inserted, regular transmissions from each DMU are logged by other nearby DMU's providing a simple form of inter-animal communication. These transmissions are recorded, allowing the pattern of social grouping to be determined.

Although the DMU's act autonomously, a base station attached to a laptop allows manual override of the device, and the downloading of logged data via wireless while in vivo. A snapshot of the current state of the device is also available in case more immediate results are required.

An overview of the entire system is presented in Figure 5.

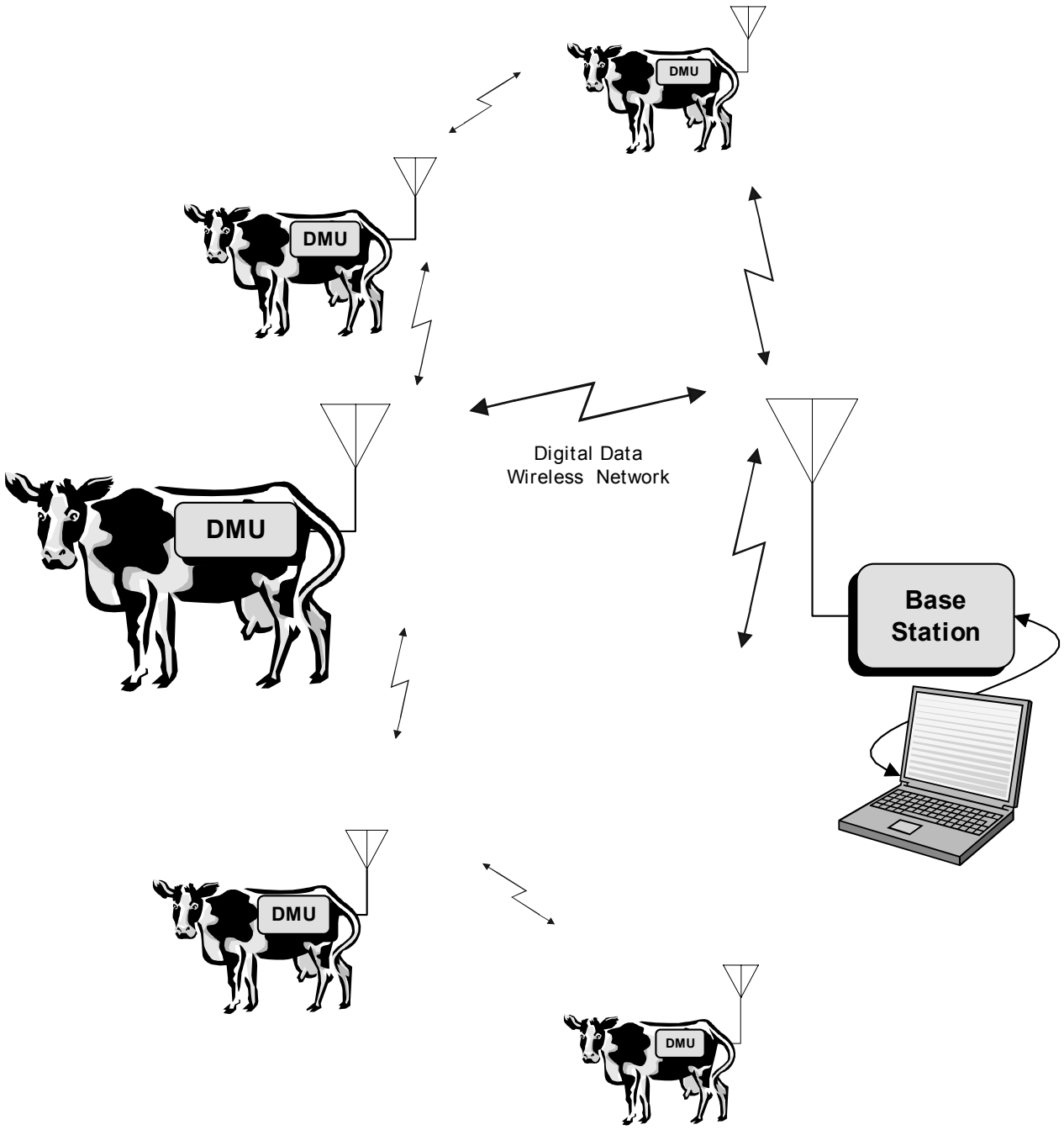


Figure 5: System Overview

The remaining discussion on DMU operation is structured in a similar way to the hierarchal DMU block diagram in Figure 6.

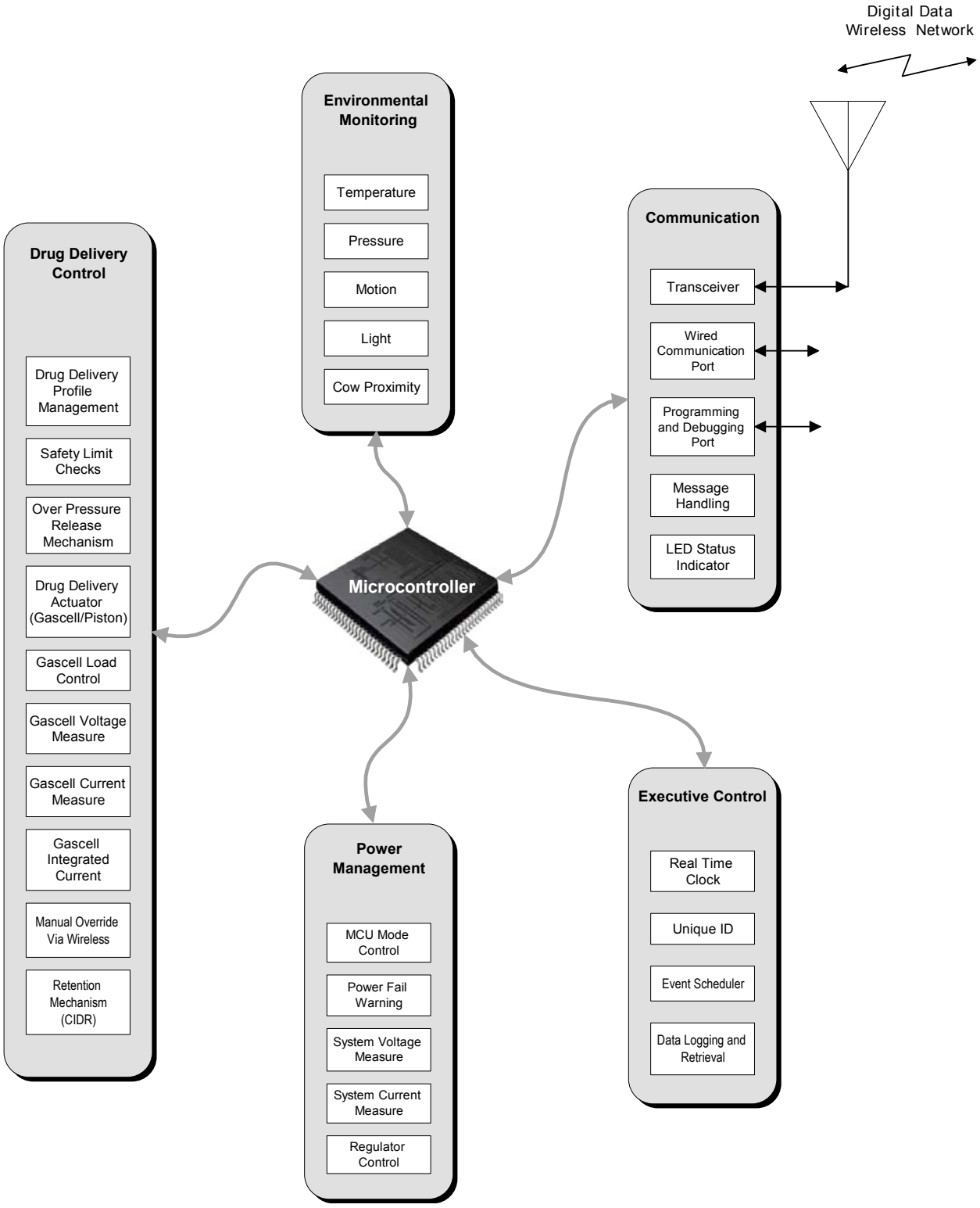


Figure 6: Block Diagram of Delivery and Monitor Unit (DMU)

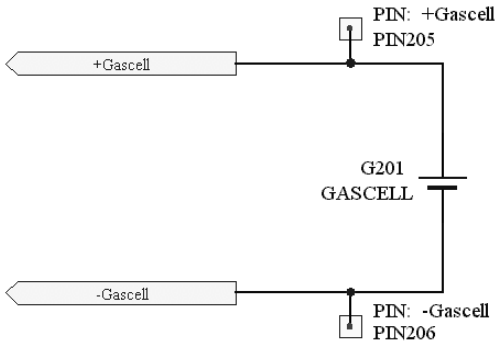
The function of each item in the block diagram is now discussed in detail. For reference, photos of the device start on page 109. Complete schematics are provided as Appendix B starting on page 177. A description of each component and its purpose is given in the DMU Bill of Materials in Appendix D starting on page 189. The PCB layout is provided in Appendix C starting on page 185.

3.5 Drug Delivery Control

3.5.1 Drug Delivery Actuator (Gascell/Piston)

The gascell needs no battery in order to produce gas: the act of drawing current is enough. Assuming other factors are constant, gas production is directly proportional to current drawn (Winsel 1993). The electrolysis action produces a constant supply of gas behind the syringe piston which propels controlled delivery of the pharmaceutical vehicle. Since the gascell is very small, this allows a large proportion of the device to be available as a drug reservoir.

In fact, the gascell does not produce hydrogen gas in a normal open air environment; it consumes oxygen instead. If activated in an enclosed space however, it starts producing hydrogen gas once all of the enclosed oxygen is depleted. For this reason, the amount of dead space in the syringe must be kept to a minimum. If there is too much dead space, a significant negative pressure is created during oxygen depletion . This means a lengthy delay for subsequent hydrogen gas production, and hence, start of delivery.



Physical	DMU Schematic
11.6mm Diameter, 4.5mm height (Simatec AG 2001)	

Figure 7: Gascell Physical and Schematic

The gascell in the DMU is represented in the schematic as G201 in Figure 7. Complete schematics are provided as Appendix B starting on page 177

There are different sized gascells available. Large ones are used in providing the piston movement in grease dispensers. Grease is supplied via a 120mL syringe attached to a standard grease nipple which obviates the need for weekly servicing on rotating machines. This can be very cost effective on inaccessible plant equipment such as pumps on marine oil rigs.

The Theratron® is a purpose built syringe incorporating the gascell originally intended for human portable drug infusion. Simatec AG (Switzerland) invented both the Theratron® and gascell. Different models are available which correspond to the particular infusion rate required. The only difference is the fixed resistor; the value of which determines the rate of delivery.

The Theratron® is a low risk technique for fluid delivery. As such, it is an ideal mechanism to deliver the pharmaceutical vehicle in the DMU.

The syringe is modified to allow the antenna transmission line to exit through the

pressure release mechanism while maintaining a (relatively) hydrogen gas tight seal. Headroom for movement above the gascell allows the whole electronics assembly to slide in relation to the rest of the syringe body should the over-pressure release cap activate. This can be seen in Figure 22 on page 110.

3.5.2 Drug Delivery Profile Management

Internal Representation of Delivery Profile

The target volume rate profile is stored as a rate of volume versus time graph inside the DMU. The actual numbers prepared by the user represent the vertices on a trace consisting of straight line segments. The smallest allowable horizontal distance of the straight line segments is one minute, allowing the graph to closely approximate any desired curve.

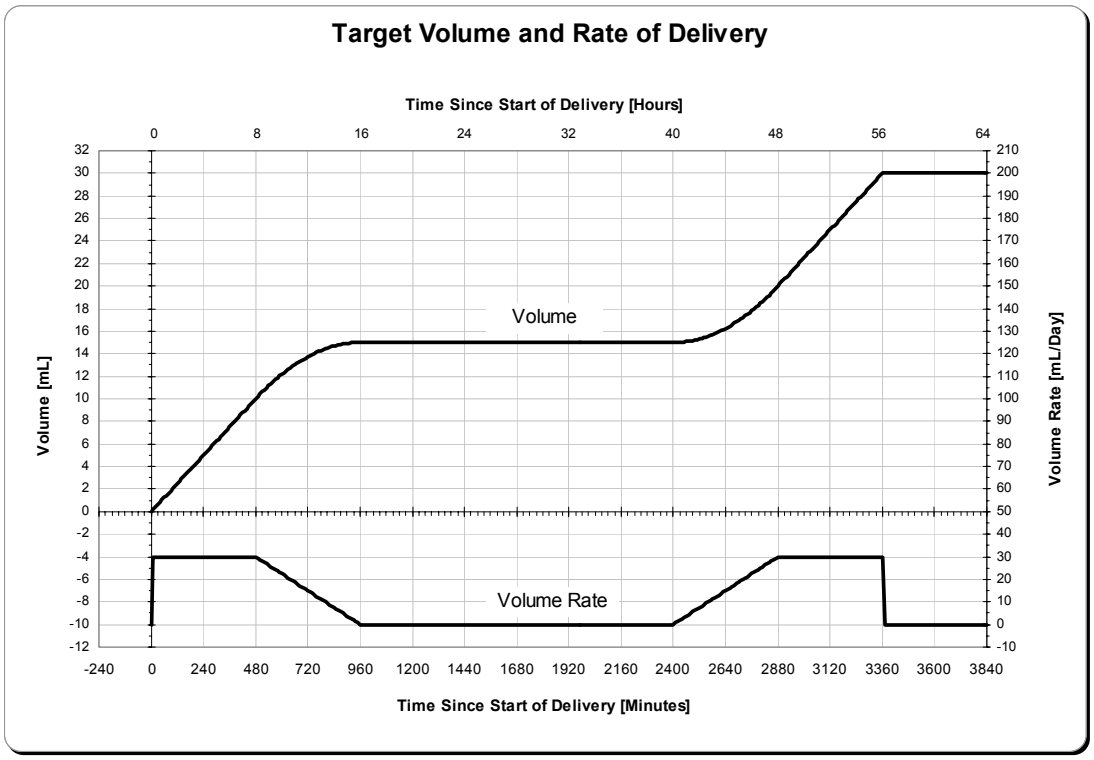


Figure 8: Sample Delivery Profile Defined on PC for Download into DMU

The volume rate trace in Figure 8 is a typical target rate profile and would be entered in the following format: `(0, 0), (1, 30), (480, 30), (960, 0), (2400, 0), (2880, 30), (3360, 30), (3361, 0), (INFINITY_MINUTES, 0)`

The list of tuples represent the vertices, where the first number in the bracket is the time in minutes, and the second number is the rate in units of mL/Day.

During system initialisation, the unique ID is used to determine which profile graph in flash memory should be pointed to for subsequent access. Routines are provided to integrate the rate profile between the current time and the start of the delivery, resulting in the instantaneous target volume to be delivered.

Start of Delivery

Assuming that all DMU's are reset and installed in syringes at the same time, the user can choose how delivery will commence:

- By relying on a set and forget trigger pressure to activate the delivery for each syringe, the syringes will deliver the most accurate amount if inserted before pressurisation has commenced. This means the start of actual drug delivery for each syringe will be slightly different due to the fact that they will take slightly different times to pressurise.

- By inserting and then relying purely on a set time delay, the syringes keep absolutely synchronised in time, but there will be some error in the amount delivered at the start of the delivery schedule.

- A more complicated approach eliminates both of the previous disadvantages. To achieve this, the syringes are keep on the bench initially. The start decision override command is made active over the wireless link until the syringe is pressurised and observed to start delivering. This keeps the gascell turned on, but prevents the profile from starting. When pressurisation occurs, the gascell override command is initiated to turn the gascell off. The syringes, are now ready to start delivery at short notice. When all syringes have been accounted for by this technique, the DMU's are inserted and both overrides are inhibited. This means they are all synchronised in time and have delivered exactly zero target and actual volume at the start of the delivery programme. The disadvantage is the extra effort required. Using this technique, many

DMU's could be prepared and stored for up to a week and be ready for this form of accurate deployment with a few minutes notice.

3.5.3 Over Pressure Release Mechanism

The blue cap (seen in Figure 22 on page 110) backs off and vents the internal cavity of the syringe should differential pressure exceed 700 ±200 mbar. If that fails to work, the entire release cap holder pops at a differential of 1100 ±100 mbar.

3.5.4 Safety Limit Checks

If body temperature or animal activity were to deviate from normal during delivery, it would be prudent to stop as soon as possible.

If a blockage occurred in the outlet of the delivery device, and the over pressure release mechanisms failed, this could have serious consequences. If the blockage frees itself after some time, the pent up pressure could deliver a bolus of drug that might prove dangerous. If the blockage did not free itself, and the syringe mechanically failed despite the two over pressure release mechanisms, sharp plastic edges might harm the animal during rupture.

If the person designing the profile made a mistake and tried to deliver more payload than is physically possible, the piston would press with increasing force against the end of the syringe at the end of the actual payload. Again, pressure would build up as if there was a blockage.

For these reasons, the gascell decision check is modified to check for out of limit readings for temperature, pressure, activity and volume delivered (see Figure 9 on page 60). If any of these factors are out of range, delivery is stopped.

3.5.5 Gascell Load Control

Variable Rate Mechanism

The gascell is connected in series with the gascell switch, load resistor and current sense resistor. The schematic is presented in Figure 52 in Appendix B on page 181.

Recall that gas production is directly proportional to current drawn, assuming temperature is constant. Some time after the electrical load on the gascell is removed, the pressurised gas finishes expanding until it is just above external atmospheric pressure. (Static piston friction prevents it from equalising completely). At this time, volume delivered is directly proportional to gas production, and hence integrated current. Hence, integrated current is used to estimate the volume delivered. The mechanism for accurately measuring integrated current is discussed in detail later. This theory includes some approximations, but they prove to be more than adequate after calibration.

To turn the fixed rate mechanism into a variable rate one requires some control circuitry. Every five minutes, the microcontroller checks the target volume against the estimated volume it has delivered. If the estimated volume is less than the target volume, the gascell is turned on. If the estimated volume is greater than the target volume, the gascell is turned off.

This is a pulsatile release mechanism, but the low pass filter effect caused by syringe piston friction turns this into a smooth dispensing action. It is a very over-damped response.

The maximum amount dispensed during a five minute period is around 300μL. Finer control is possible by decreasing the gascell decision period. An alternative would be to increase the value of the load resistor, but this would decrease the maximum attainable rate of delivery. Note that the resolution of measured estimated volume delivered is much finer than 300μL (discussed later).

This is a closed loop control system. Variability in gascell condition and the

value of the load resistor are automatically compensated for. The only significant errors in gas production volume are measurement of the integrated current, and any syringe behaviour (leaking gas etc.). A slightly defective gascell will produce just as accurate a result; it will simply be told to turn on more often to make up for the short fall in expected current while on. The practical significance of this is that each gascell can be used twice, as long as particularly high volume delivery rates are not required on the second use .

Gascell Switch Decision

The gascell switch decision made by the dispensing scheduler can be overridden by external manual control over the wireless link. The exception is when the external command tries to turn the gascell on while safety limits are exceeded. Safety checks always have the highest priority.

Figure 9 is a simplified flowchart. The actual decision making process is complicated by the routines for managing the start of programmed delivery and implementing various diagnostics modes.

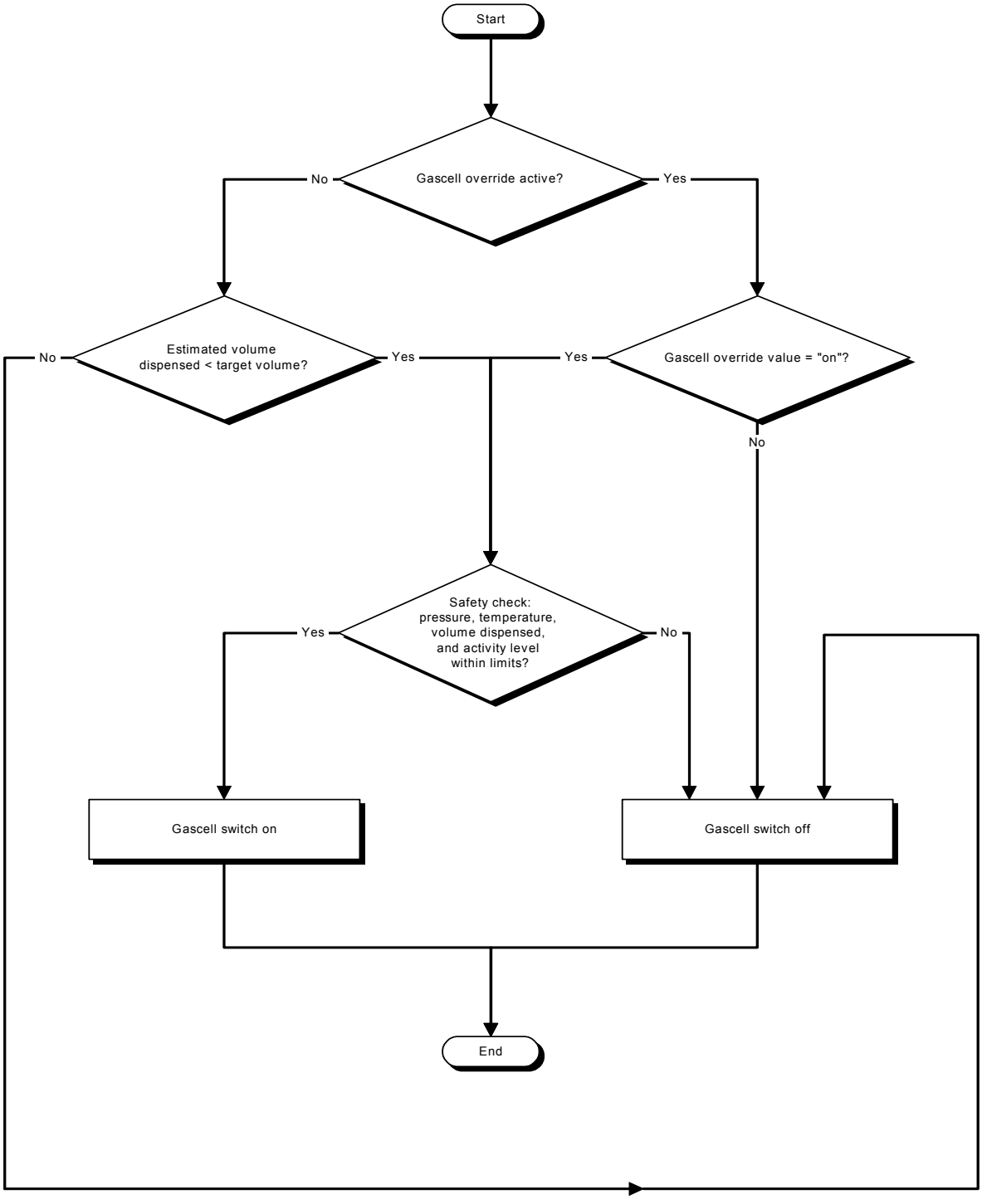


Figure 9: DMU Gascell Switch Decision

Pressure Leak Compensation

Hydrogen gas molecules are extremely small, and given time, can even penetrate thick glass. It is next to impossible to stop the hydrogen gas leaking slowly from the O-ring sealed plastic syringe.

Escaping hydrogen gas would lead to a shortfall of delivered drug volume. To counter this, a rudimentary form of pressure leak compensation is employed: If the pressure drops too low during periods of zero-rate delivery, the gascell is turned on until the pressure increases to the value just short of moving the piston. During this compensation behaviour, the integrating current accumulator is not incremented.

Unfortunately, the syringe leaks at an even greater rate at non-zero rates of delivery because the pressure is higher. This can be taken account of by considering it as part of the integrated-current-to-volume-delivered ratio. At 38.6°C, for every 3 mAhr of integrated current produced, there is about 1 mL of drug delivered. The assumption here is that the gas leak rate is constant for different internal/external differential pressures. This is untrue, but turns out to be a good enough approximation in practice.

A more accurate method would be to maintain another integrating current accumulator representing estimated total lost gas. This "leak compensation" accumulator would be incremented by the full amount during the zero-rate delivery period. I.e., it would accumulate when the pressure is being topped up to keep it at the pressure just below which the piston would move, as in the rudimentary scheme. In addition, it would be incremented to some extent during the non-zero rates of delivery. The actual pressure readings are read and stored every 15 minutes, so this pressure reading could then be turned into an instantaneous leak rate prediction through a look-up table. Integration of this would result in a better estimate of the hydrogen gas leakage for any profile. The "leak compensation" accumulator is subtracted from the "gas produced" integrated current accumulator to provide a more accurate estimate of amount delivered.

This more complicated method was not attempted because the rudimentary effort proved surprisingly accurate. The estimated and actual volumes delivered in Figure 25 on page 114 are within 3% even though the profile is a demanding one. Accuracy is more than adequate, even though the profile involves lengthy periods of zero-rate delivery and delivery at different rates.

Syringe Calibration

Each syringe/piston set has a different leak rate and piston friction coefficient due to dimensional manufacturing tolerances and wear. The variance of these factors can be reduced to an acceptable level by the use of two methods:

- Piston lubrication with silicone oil: Careful attention to consistent application of silicone oil to the piston results in reducing the variance in piston friction.

- Calibration constants for piston friction and leak rate: The leak rate and moving piston friction coefficients are combined with the integrated-current-to-volume-delivered ratio. This is explained in the section on leak compensation above. The variance in static piston friction is partly eliminated by specifying an individual minimum pressure leak compensation limit for each syringe/piston set.

The calibration process is straight forward: The sample run is performed with the desired syringe/piston set and a very low pressure leak compensation threshold. To determine the leak rate factor, the data is scaled in a spreadsheet until the actual delivered volume overlays the target delivered volume. The integrated current to volume dispensed ratio is then altered by this empirically determined scale factor.

The calibration factors for each individual unit are stored in flash memory. They are selected using the machine readable ID number during power on reset initialisation.

The pressure threshold at which to first apply leak compensation is determined simply by looking at the pressure trace during a zero delivery period to determine

where the volume just stopped being delivered.

3.5.6 Gascell Voltage Measure

The voltage on the gascell varies between 0.4 and 1.8V depending on the composition of surrounding gas, load on the cell and remaining capacity. Gascell voltage is logged for diagnostic purposes only.

3.5.7 Gascell Current Measure

Instantaneous gascell current is, likewise, logged for diagnostic purposes only. This happens once every 15 minutes and should not be confused with gascell current integration discussed next.

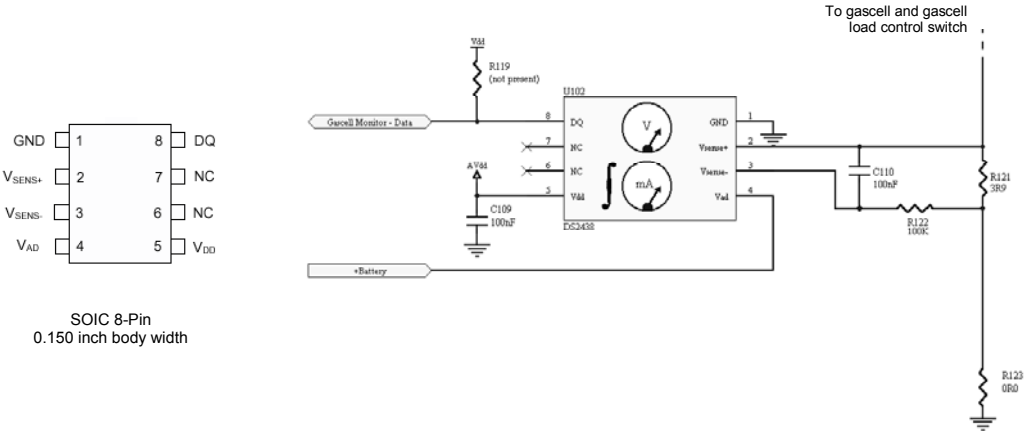
3.5.8 Gascell Integrated Current

Gascell integrated current is used to provide an estimate of how much volume has been dispensed. With the gascell turned on, current flows through the gascell current sense resistor (R121 in Figure 10). A voltage is developed across this resistor which is measured to find instantaneous gascell current. Although this resistor has a rather large 2% manufacturing tolerance, the effective tolerance is much lower. This is achieved by measuring its value accurately during DMU assembly, and storing this with the other calibration constants. C110 and R122 form a low pass filter to help capture the effect of any particularly fast current transients.

The DS2438 gascell monitor IC (U102 in the same figure) was originally developed for fuel gauging battery packs in cell phones. It has the following features:

- Unique serial number.
- Direct to digital temperature sensor.
- Real time clock.
- Two general purpose analogue to digital voltage inputs.
- Integrated current accumulator: Keeps a running total of all current going into and out of the battery.
- 40 bytes of non-volatile memory (EEPROM).

All these functions are provided in an 8 pin small outline IC format. Communication with the device is via a bi-directional one wire serial bus: the DQ line. Only the integrated current accumulator is used for integrated gascell current measurements. The other functions of the gascell monitor IC will be discussed as they become relevant.



Physical DMU Schematic

Figure 10: Gascell Monitor Physical and Schematic

The accuracy of delivery relies heavily on obtaining accurate integrated current measurements. This is complicated by the fact that gascell current varies somewhat with a constant resistive load due to bubbles that form on the gascell electrodes. To combat this, the instantaneous current is measured and accumulated 36 times a second with the gascell monitor IC 10-bit analogue to digital converter. This occurs even when the microcontroller is asleep, consuming only 30μA of battery current on average.

The voltage resolution of the integrating current analogue to digital converter is 244.1μV which translates into a current of 62μA. Sampling and accumulating at 36Hz, this would represent a theoretical estimated volume resolution of less than 1nL. Nano-litre accuracy is unattainable in practice due to analogue to digital converter error, thermal and semiconductor noise, residual error on the sense resistor and analogue to digital conversion errors. Variability of piston friction and other physical attributes of the syringe swamp any attempt to make use of such a fine resolution. The bench test results proved that the short term resolution of the overall system is on the order of 10μL. A graph of bench test delivery is presented on page 114.

Threshold

When the gascell supplies very little current, the error after offset correction due to the current analogue to digital converter is still ±2 least significant bits. This means that measurements of very small currents can be inaccurate by a high percentage. Integrated over a long time, these inaccuracies can turn into large errors. The DS2438 monitor IC provides a method for filtering out potentially erroneous small signals so that they are not accumulated. If the current is less than two least significant bits, it is not accumulated, however if it is over two least significant bits, it is accumulated with full accuracy.

Calibration

Being only 3.9 Ohms, the voltage across the current sense resistor is small in terms of the potential DC offset error of a typical analogue to digital converter

input op-amp. The effect of DC offset error is minimized by calibrating it out every 40 minutes. This is achieved by reading the no-load error current and storing the negative value of that in the DC offset error register. Whenever the gascell monitor IC takes a current measurement (36 times a second), it adds the value in the DC offset error register to the result before accumulating it.

3.5.9 Manual Override Via Wireless

The gascell load can be switched on or off manually over the wireless link, subject to the safety check. The delivery profile can also be controlled by a manual over ride, suspending or resetting the delivery schedule.

3.5.10 Retention Mechanism

To retain the DMU in the vagina, a CIDR® device (see Glossary) is attached to the syringe with adhesive and tape. Being loaded with progesterone, it prevents the cow from coming into estrus. A blank CIDR® with no progesterone can be used if this effect is undesirable.

3.6 Power Management

3.6.1 Batteries

Button cells were chosen for the power source. Three Energizer EPX76 silver oxide (Zn/Ag_20) batteries in series give a fairly flat discharge profile at a nominal on load voltage 4.5V. These are represented in the DMU schematic as B201, B202 and B203 in Figure 53 on page 182. The batteries are the same size and shape as the gascell. There were no suitable battery clips available, so they were fabricated from strips of 0.9mm brass sheet.

3.6.2 Low Voltage Power Supply Considerations

The voltage from the batteries is regulated to 3V. There are advantages and

disadvantages operating at 3V. On the plus side, operating from 3V instead of 5V decreases current consumption by 40%. Battery life increases by more than 40% because batteries have a higher effective capacity at a lower discharge rate. More importantly, power consumption increases as the square of the operating voltage, so reducing the operating voltage of a device from 5V to 3V decreases power consumption by 64%.

Heat production is reduced, which is important when trying to accurately measure body temperature from within the small enclosed space of the syringe body. Current leakage from power supply decoupling capacitors and IC output pins is also reduced.

Noise margins at inputs are lower, however the sources of on-board noise generators are reduced. For example, ground bounce from high speed switching is reduced due to the lower aiming voltage of the switching device. This means less spurious RF emissions (Williams 1993, Application Note AP-477).

There are some disadvantages:

- Noise due to externally induced currents has increased ability to corrupt signal levels.
- 3V devices are more fragile: CMOS 3V devices have thinner silicon oxide gate layers making them more susceptible to electrostatic damage.
- 3V parts are usually de-rated in terms of speed due to the thinner gate layers increasing the capacitance. The maximum speed of the chosen 3V microcontroller is 10MHz, compared to its 5V counterpart which can go to 16MHz.

In summary, although there is less noise immunity and a reduced maximum microcontroller clocking speed imposed by the system-wide 3V power supply choice, this is greatly outweighed by the increased battery life and the fact that less cells in series are required to achieve the required battery operating voltage.

3.6.3 Microcontroller Mode Control

To get a useful life out the batteries, careful control of the power state of the microcontroller and other IC's in the circuit is required. Figure 11 depicts the various power management modes the circuit can be in. The modes are the shaded boxes and give the amount of current consumed for the whole circuit while in that mode, as well as the percentage of time spent there. The microcontroller port pins configure peripherals for lowest power consumption at all times. The mode transition causes are represented by arrows.

This is a simplified view of how mode switching occurs. It is impossible to accurately show on one page what happens for each individual state and every possible combination of interrupt event.

Table 1: Description of Microcontroller Modes

Mode	Description
Sleep	Microcontroller core stopped, timers being clocked by 32kHz sub-clock for real time clock and motion activity counters, gascell current integration 36 times a second, transceiver in sleep mode. 10MHz oscillator is off.
Doze	As for sleep mode, but transceiver is in receive mode.
Low Speed	As for doze mode but microcontroller core is operating from 32kHz sub-clock.
Fully Awake	Microcontroller core is clocked from 10MHz oscillator. Transceiver is in receive or transmit mode.

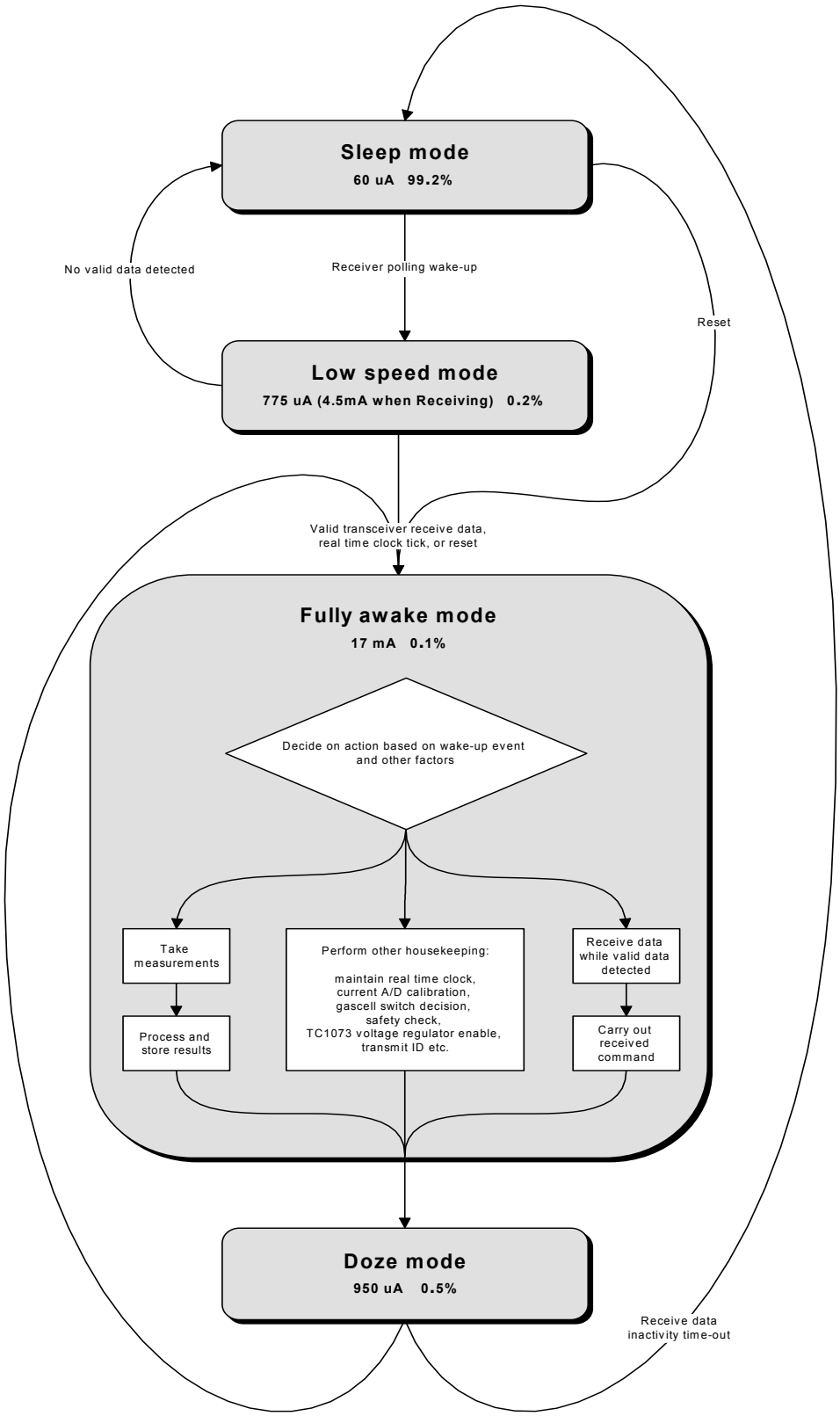


Figure 11: Power Mode Control

Current Consumption in Sleep Mode

The transceiver draws too much current to be kept waiting for data in receive mode. Instead, it is placed in receive mode for only 8ms out of every 600ms. It is asleep for the remaining part of the receive polling cycle. The average current due purely to receiver polling is:

duty cycle x (receive current + microcontroller low speed current)
= 8ms / 600ms x (3.7mA + 0.78mA)
= 60μA

The total sleep current for the entire circuit when the transceiver is off is 60μA. With receive polling this increases total sleep mode circuit current consumption to 120μA.

Ideally, pulse width modulation outputs would have been used to control receive mode polling. This would have eliminated the need for the microcontroller to wake up once every second to initiate the "on" part of the receiver polling cycle.

When the gascell is off, the microcontroller takes the DQ line low before entering sleep mode. This puts the gascell monitor in a low power mode where only the real-time clock functions. (The battery monitor has it own real-time clock.) This saves power without affecting integrated current measurements.

Although it may appear on the DMU schematic diagrams in Appendix B that spare microcontroller IO pins have been left floating, that is not the case. All unconnected IO pins are configured as outputs which reduces the current per pin to around 50nA.

Table 2 gives the measured current from all parts of the device in sleep mode.

Table 2: Current Consumption in Sleep Mode

Item	Comments	Current (μA)
Microcontroller	Wait mode with two timers and one counter on, some hardware interrupts enabled, 32kHz oscillator in high drive mode, 10MHz oscillator off.	3
Receiver polling	Duty cycle operation: receive mode for 8ms, sleep mode for rest of the 600ms cycle. Average current is 60μA.	60
Power supply decoupling capacitors	Leakage current	2
Gascell monitor	Assumes monitor is in low power mode about 80% of the time. The monitor draws 32μA if on, 22μA in shutdown.	29
Regulator combined ground currents	TC1073 regulator in shutdown. Add 48μA if TC1073 regulator is on. This occurs when the batteries reach the last 20% of their useful life.	8
Reset IC input bias network		2
Reset IC		4
Pressure transducer		1
Gascell switch		1
Leakage on spare microcontroller IO pins		4
Zener diode reverse leakage		2
Light sensor LDR bias		3
	Total	119μA

Current Consumption in Fully Awake Mode

With the microcontroller fully awake, transceiver mode polling no longer occurs. The transceiver is either in transmit mode or receive mode. The following table summarises the changes in current draw when the microcontroller is fully awake.

Table 3: Current Consumption in Fully Awake Mode

Item	Comments	Current (mA)
Microcontroller	10MHz, running at divide by 1, no-wait bus cycle.	8
Transceiver	Transmitting: 10mA peak, 6mA average. Receiving: 4mA Overall average: 5mA.	5
LED		3
Other activity including all loads present in sleep mode		1
	Total	17mA

3.6.4 Power Fail Warning

A brown out is always terminated by a proper reset signal, rather than the Vdd simply dropping below that required for reliable operation. This function is provided by the reset generator: U106 in Figure 51 on page180. The reset delay is chosen so that if the batteries were suddenly disconnected, stored energy in the power supply capacitors would allow operation at full clock speed to occur for at least 1.7ms (17 000 clock cycles). This gives the power fail interrupt routine enough time to store important data to non-volatile memory and write an error log entry before the system is reset. The first task for the power fail interrupt service routine is to turn off any peripherals. The reduced current results in the reset delay extending to 5ms before hardware reset occurs.

3.6.5 Watchdog

There is a watchdog timer on board the microcontroller which can be used to recover from code crashes. Important data such as unexpected reset events, elapsed time and delivery profile progress markers, can be saved to non-volatile memory during the watchdog interrupt service routine before a reset is issued.

Watchdog resets are logged for diagnostic purposes.

3.6.6 System Voltage Measure

Battery voltage is logged for diagnostic purposes.

3.6.7 System Current Measure

Battery current is logged for diagnostic purposes.

3.6.8 Voltage Regulators

The 3.0V voltage regulators provide a stable supply voltage from the batteries as they discharge. Normally, the batteries are well above 3.0V, but to obtain the longest possible battery life, the regulators operate in drop-out out mode when the batteries drop below this level, supplying as much voltage as possible.

In retrospect, it would have been prudent to power the RF board off a separate voltage regulator to reduce noise into the receiver from the switching in the digital board. Fortunately, the circuit works adequately, given the power filtering and decoupling suggested in transceiver IC datasheet.

Regulator Control

Very low quiescent current and dropout voltage from the voltage regulator is a requirement for long battery life. Quiescent current is the current in the regulator ground pin that is essentially wasted. Since the voltage regulator is always connected to the batteries, it must be an absolute minimum to prolong battery life.

In simplified terms, dropout voltage is the voltage difference across the regulator when the battery starts to run low. The higher the drop out voltage, the higher the minimum battery voltage required for reliable operation. A lower dropout voltage translates into extra battery life when the batteries begin to go flat.

The two regulators are U107 and U108 in Figure 51 on page 180. The Complementary Metal Oxide Semiconductor (CMOS) TelCom TC1073 regulator (U108) has an unacceptably high 50μA quiescent current when operating, but an excellent 25mV dropout voltage at 30mA load. The Motorola MC78FC30

regulator (U107) has a very low 7μA quiescent current, but an unacceptably high dropout voltage. The solution is to use both.

The TC1073 has a shutdown function which turns it off. This reduces quiescent current to <0.1μA. When the batteries are low, it is switched on, reducing the dropout voltage over the MC78FC30. There was some doubt as to whether this would result in a correct design. Application advice from the voltage regulator design team at TelCom resolved the issue and it works very well in practice.

The TC1073 also has a low battery voltage "error" pin which can be used for an asynchronous power failure interrupt when it is enabled. The active state and error pin status of the TC1073 are logged for diagnostic purposes.

3.7 Communication

3.7.1 Communication Medium

Various mediums were evaluated for this application which requires a non-contact range of 30m in the presence of industrial noise found in the milking parlour environment along with the special needs of the device to operate while being almost entirely inside the cow.

Optical/Infra-red

Optical links have been used successfully in the past to transmit information from in vivo through a thin layer of skin and flesh (Lindsey et al. 1998, 45:614-619). However, the most practical way to implement an optical link would be to have a protruding sensor and emitter since this is allowed.

The specification calls for a device capable of working through a layer of mud and faeces. These materials are opaque to visible and infra-red light, and so infra-red is unsuitable in this application whether embedded or protruding.

Ionic Conduction

This is a novel technique whereby the bodily fluids themselves carry the modulated current induced by the transmitter (Lindsey, McKee, Hull, and Howell 1998, 45:614-619). Electrodes need only be placed on the surface of the skin without penetration to effect communication with an embedded device. This a technique requiring direct contact, mentioned more for interest than for consideration in this application.

A cow ID system using this technique has been developed and uses the farmer's body to complete the connection between cow and reader. There were some problems reported with communications failure during drier times of the year. In addition, cows are very sensitive to stray voltage and can be irritated by as little as 4V, having an unusually low impedance to earth.

Ultrasound

Cheap ultrasonic transponders would not tolerate being submersed and their frequency of operation would be affected even if not permanently damaged.

Inductive/Capacitive Coupling

The inductive technique is a well proven data transmission method for embedded biotelemetry devices (Jeutter 1983, 2:17-24). Nevertheless, these are short-range effects used effectively over a distance of only three metres (at most) with miniaturized circuits. As such it is unsuitable for the current application requiring longer range. However, this method of communication might be well suited to a device, in say, the rumen, if short range can be tolerated.

The inductive method of communication has the advantage of being able to penetrate thick flesh with little extra attenuation. This method of communication has now been packaged neatly for rapid application to the general task of short range, high data rate, two-way wireless communications in a product called LibertyLink from Aura Communications (Aura Communications Inc. 2001). This takes the form of small chip and antenna ready to be connected to an existing microcontroller. Having negligible electric field component, licensing by

electromagnetic spectrum management agencies is easy to obtain worldwide.

A variation on inductive coupling is a method termed *load shift keying* where the implanted circuit gains power from an inductively coupled source. The implant alters the impedance of its receiving coil which varies the voltage across the RF coil in the external power source/data reader. As expected, this method has a range of only a few centimetres, but has been successfully demonstrated in a patient based application where the hand grasp function was restored to a partial quadriplegic (Tang et al. 1995, 42:524-528)

Because the range of inductive and capacitance effects are not far enough, these methods of communication were ruled out for this particular application, although it is perhaps the best solution for a device situated in the rumen.

Electromagnetic Radio Frequency Waves

Electromagnetic waves in the Radio Frequency (RF) spectrum can penetrate a thin layer of mud, water and other partially conductive materials at up to 1 GHz. Cheap transmitters are commonly used in such applications as car alarm activation keys and garage door openers. These typically have ranges in excess of 50m and are mass produced in low cost, moderate performing systems.

One commercial device has been developed for animal identification and temperature recording for the purposes of animal health and possible estrus detection. This is a device to be located in the rumen using two-way RF communication with a read range of about 3m (Magtrac Inc. 2001). Later developments were going to add satellite boluses that could be ingested to magnetically attach to a permanently resident iron core. Dispenser satellites for antibiotics, worming and data storage would have been developed, but the product has since been discontinued for unknown reasons.

Previous experimental work demonstrated another device operating at 418MHz from inside a human vagina which had an effective operating range of 10m (McCreesh and Evans 1994:904-905;Scanlon, Evans, and McCreesh 1997, 44:427-430). Bergen (1997) also had success from transmitting RF at 27MHz

from the retro-peritoneal space inside a monkey. Likewise, a commercially available telemetry device operating at 303.8MHz was used successfully to transmit glucose monitor data in vivo for a distance of 7m (Beach, Kuster, and Moussy 1999, 48:1239-1245). This experiment used a digital form of transmission known as on/off keying.

A frequency of 4MHz was used successfully in an implantable intracorporal pressure and temperature application in humans with dimensions of only 6x28x2mm. Range was only 5mm due mostly to the restricted space available for the antenna (Flick and Orglmeister 2000, 47:12-16).

A frequency of 86 to 88 MHz was used in an implantable transmitter for the purposes of subcutaneously monitoring glucose in dogs (Shults et al. 1994, 41:937-942). This worked well when implanted in thoracic subcutaneous tissue. Both frequency and amplitude modulation were trailed with amplitude modulation giving the best range of 10m.

RF is the only proven method of communication established in the literature for data transmission from within body cavities with a range in excess of 5m and so was chosen for this application.

3.7.2 Licensing

There are restrictions in New Zealand and other countries on the use of the electromagnetic spectrum with the aim of avoiding interference with other users. This is achieved by licensing, which is a potentially complicated and expensive process. To alleviate this, the DMU is designed to comply with the description for a *Restricted Radiation Device* as defined by the Radio Spectrum Management Department of the Ministry of Commerce in New Zealand.

These devices require a declaration of conformity to level 1 under Schedule 1A of RFS 29 “Specification for Restricted Radiation Radio Apparatus” (Radio Spectrum Management Department of the Ministry of Commerce 1998). Falling under the “general” license, this means that no individual licensing is required from the end-user's point of view. In particular, the DMU falls under level 1:

"consumer appliances", not level 2: "radio products" because it is covered by the definition of "low power apparatus". To meet the licensing requirements, an independent facility carries out tests in accordance with the regulations and prepares a report. A declaration of conformity is lodged with the Ministry of Commerce and the applicant may be required to prove the conformity in a more rigorous manner if randomly selected as part of the quality control auditing process.

Complying with the Restricted Radiation Device format sets limits on frequency of use, power output and duty cycle of transmission. Matching the restrictions in Part 1 of Schedule 1A against desired technical performance of otherwise suitable devices defined the allowable operational limits:

- Frequency: 433.700 to 434.100 MHz
- Modulation: Any.
- Usage: Telemetry/Telecontrol
- Maximum Power output: 1mW (effective isotropic radiant power).

Many other combinations of operational limits would have been suitable, but the best transceiver judged on technical merit is only available at set frequencies, so this factor defined exactly how the regulations applied to the rest of the parameters.

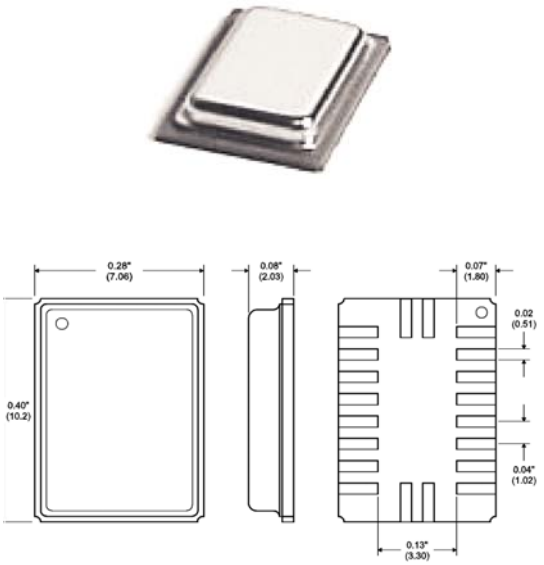
3.7.3 Transceiver Hybrid

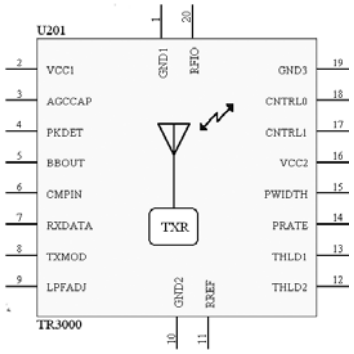
Transceiver Selection

The TR3000 amplifier sequenced hybrid transceiver IC from RF Monolithics was chosen as the hardware to carry out the transceiver task. This is designated U201 and shown by itself in Figure 12 immediately below. The full transceiver board incorporating the transceiver hybrid is shown in Figure 53 on page 182.

The TR3000 was the only device that complied with the Restricted Radiation Device regulations, fitted in the restricted physical space, and was integrated

enough to easily form part of a circuit with the minimum amount of components. It also meets the minimum requirements for data rate, power consumption, availability of technical support and ease of development.





Physical
(Dimensions in inches and mm)
(RF Monolithics Inc. 2001)

DMU Schematic

Figure 12: Transceiver Hybrid Physical and Schematic

Being of fixed carrier frequency, the part number determines the frequency of operation. The TR3000 is one of only two part numbers to have a frequency that falls inside one of the regulatory New Zealand bandwidths. This device uses amplitude shift keying or on/off keying at a carrier of 433.92MHz. On/off keying was selected because the amplitude shift keying mode is only available at higher data rates which have correspondingly reduced range. These transceivers have been used in products to track climbers on Mt. Everest and runners in the Boston Marathon.

Amplifier Sequenced Hybrid Design Theory

The Amplifier Sequenced Hybrid (ASH) design employed in the TR3000 contains

an amplifier time-sequenced receiver section which provides over 90 dB of RF gain without the use of frequency down conversion. Unlike a superheterodyne receiver which achieves stability by distributing RF gain over multiple frequencies, the ASH transceiver distributes the total RF gain over time.

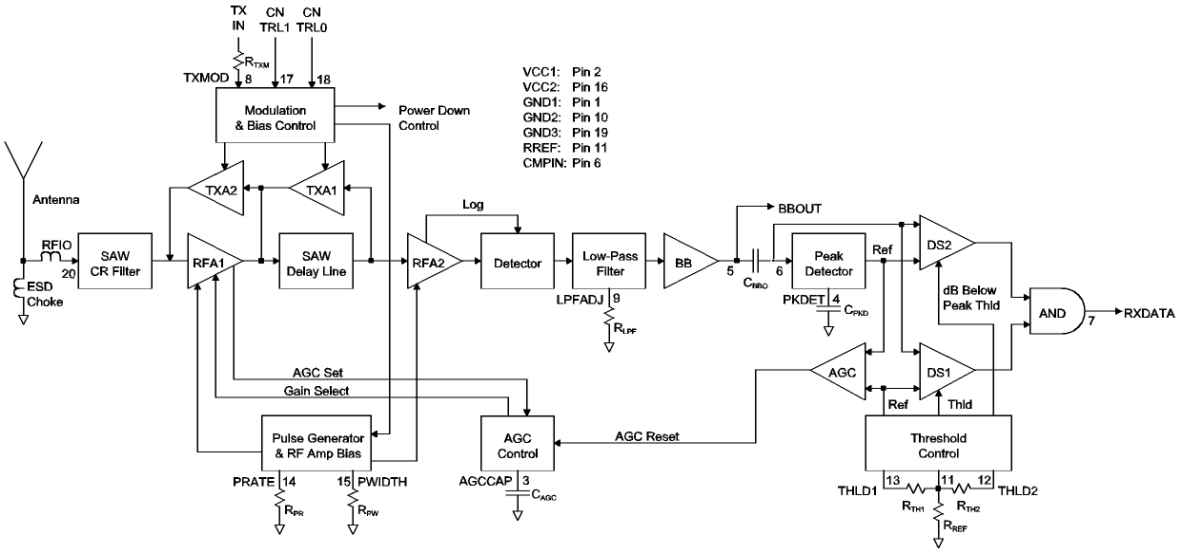


Figure 13: Amplifier Sequenced Hybrid Transceiver Block Diagram
(RF Monolithics Inc. 2001)

In receive mode, RF amplifiers RFA1 and RFA2 are controlled by a pulse generator, and the two amplifiers are coupled by a surface acoustic wave delay line. The RF signal is filtered by a narrow-band surface acoustic wave filter before RFA1 to eliminate noise outside the pass band. The pulse generator turns RFA1 on and RFA2 off. After being amplified by RFA1, the signal travels along the delay line. Now RFA1 is off and RFA2 is on, applying more gain. RFA1 and RFA2 are never on at the same time resulting in excellent feedback isolation. The architecture leads itself to very quick power up and power down times.

A wide dynamic range log detector, digital automatic gain control and a compound data slicer are built in. The delay line and surface acoustic wave filter are used for both the receive and transmit functions.

Transceiver Hybrid Configuration

The TR3000 transceiver IC can be set up for various transmit power, receiver

sensitivity, modulation type and depth, minimum symbol width, maximum run length, data slicer behaviour, automatic gain control and squelch threshold level configurations through the choice of external components. In this application, the transceiver is configured for on/off keying modulation at a 23k Bits Per Second (BPS).

Transceiver Polling

As explained in the power mode control section, the transceiver draws too much current to be kept waiting in receive mode. Instead, the transceiver is placed in receive mode for 8ms out of every 600ms. It is asleep for the remaining part of the receive polling cycle.

When DMU or base station wants to send a message, it transmits a 800ms preamble before the first packet. This 'tickle' wakes up all DMU's in range and keeps them awake and in full-time receive mode until they detect 2.5 seconds of continuous silence. They then re-enter sleep mode to continue receiver polling (see Figure 11).

The potential problem with this scheme is that internally generated receiver noise periodically generates a spike about once every second, even with a moderate squelch threshold. Other electromagnetic radiators in the area such as electric fences and cell phones can also cause spikes. Noise spikes could keep the DMU permanently awake, depleting the batteries within an hour or so.

The solution was to implement a noise spike rejection algorithm. This was simply a matter of sampling the receive data line a few times in a row and making sure that the data stream consisted of zeroes and ones, instead of just spikes. With the noise spike rejection algorithm in place, a transmitting digital cell phone did not keep the transceiver awake unless brought within 5cm of the DMU antenna. Before noise spike rejection, this distance had been up to 1m.

3.7.4 Channel Encoding

The wireless channel is a hostile environment. Multi-path interference and noise contribute to degrade signal quality at the receiver. The multi-path problem lies in

the fact that the signal can take more than one path from transmitter to receiver. Different paths have different path lengths, so these signal components arrive out of phase with one another, sometimes cancelling, sometimes re-enforcing. The result is a sporadic fast fading attenuation that can generate erroneous bits in the data stream, even when the average signal strength is relatively high.

Amplified semiconductor and thermal noise, noise from man-made or artificial sources, and other transmitters in the area can also cause bit errors. In the dairy farm environment there are many industrial electric motors for powering everything from vacuum pumps to drench mixers. A rotary milking platform has a set of rotating glands with slip rings to transfer the power to the moving platform which is a another potential problem area. Each electric fence and its associated controller is a very effective transmitter of electromagnetic radiation. The wiring in the fence acts as an antenna, extending a great distance around the farm. Even though most of the interference is comparatively low in frequency, the switching noise is audible on telephone circuits and radios in the vicinity.

Another consideration is that the reception process introduces a limitation in the patterns of data that can be used. The data slicer in the receiver is preceded by a low pass filter to limit the effect of noise spikes, and coupled via a capacitor to provide adequate dynamic range. This imposes a base band limited constraint on the data stream. The minimum bit width must be wide enough to pass through the low pass filter, setting the maximum bit rate. However, the data value must also change frequently so that the high pass filter effect of the coupling capacitor does not let the data slicer settle to an indeterminate state representing a value halfway between a zero and a one.

If the base band filter requirements and bit errors are ignored, then the system would become practically useless. Fortunately, the information bits transmitted over a digital wireless link can be protected by introducing redundant bits and rearranging them into a more palatable data stream. This collective process is known as channel coding. In summary, the aims of channel encoding are to:

- Provide error checking, possibly in combination with error correction.

- Provide control codes that can be differentiated from the data.
- Achieve DC balance.
- Provide a minimum run length.
- Be easy to implement.
- Be efficient compared to other encoding methods.

Channel encoding should be preceded by source encoding. Source encoding is the process of using a digital signal to represent an original analogue signal generated from an input transducer. In a digital cell phone, the analogue output from the microphone is translated into digital numbers before being transmitted. It is assumed here that source coding and data compression have already been performed.

Each stage of channel encoding is now discussed in the order in which it is performed at the sending end. The inverse of these operations is performed at the receiving end in reverse order to recover the original data.

The data is best treated as blocks of bits called packets. By limiting the packet size, the amount of information that needs to be resent when an unrecoverable error occurs is minimized. If the packets are too small, however, there is unnecessary overhead in the percentage of bits used to manage the packetisation process. Long messages are split up into numbered packets to be stitched together again at the other end. The packet structure and encoding described below applies to each packet individually.

Cyclic Redundancy Check

It is essential to know if the data has been received without corruption. In the case of the Cyclic Redundancy Check (CRC), this is achieved by appending redundant bits to the end of the payload. A linear feedback shift register implements a polynomial algorithm to generate a 16 bit field that is sent along with the data. The polynomial used in the hardware CRC unit on the microcontroller in the DMU is the CCITT standard polynomial which catches all

burst bit errors of 16 bits or less and all longer bursts with 99.998% probability.

Forward Error Correction

Systems which detect errors during transmission and simply ask for data to be resent can suffer from excessive numbers of retries and collisions. The more retries which occur, the more likely it is that further collisions and retries will occur. Sufficient error detection is performed by the use of the cyclic redundancy check, however, it is possible to add the capability to correct for some of these errors without the need for resending. By employing Forward Error Correction (FEC) additional information is sent along with the data bytes to be transmitted allowing the receiving device to detect and attempt to correct for some or all of these errors.

In the proposed channel encoding scheme, a simple block code is used where every group of six bytes has two bytes of redundancy added. This allows correction of all single errors, and all two bit adjacent errors. A bit error rate improvement of between 3dB and 10dB can be achieved by forward error correction.

Interleaving

Next comes interleaving. Errors usually occur in bursts in a wireless environment so the interleaver rearranges the order of the encoded data bits so that these errors are widely dispersed. After decoding at the receiver, these burst errors appear as widely spread random errors that fall within the error correcting capability of the forward error correcting code. The simplest way to achieve this is to read the data stream into a grid row by row, and send it out column by column.

Coding for Minimum Run Length and DC Balance

The data slicer in the receiver is coupled via a capacitor, introducing a high pass filter effect. This allows the intended logic value to be predicted by looking at the short run average value of the received signal, with greatest weighting on the most recently received bit period.

This imposes two restraints on the data pattern: It must be guaranteed to have frequent state transitions, and it must be DC balanced. If long strings of zeros or long strings of ones were sent in a row, the high pass filter output would settle down to an indeterminate value between the voltages representing zero and one, corrupting the data stream. Frequent bit transitions are also necessary for the receiver to maintain synchronisation with the transmitter. The maximum run length in the DMU has been set to five to provide a compromise between high bit rate and greater sensitivity.

Figure 14 shows the receiver signal processing in a simplified form. Any data slicer input voltage below 0V is converted to a zero at the "Data Out" port, and any voltage above 0V is converted to a one. A change from zero to one lifts it moderately towards +1, and a change from one to zero drags it moderately down towards –1.

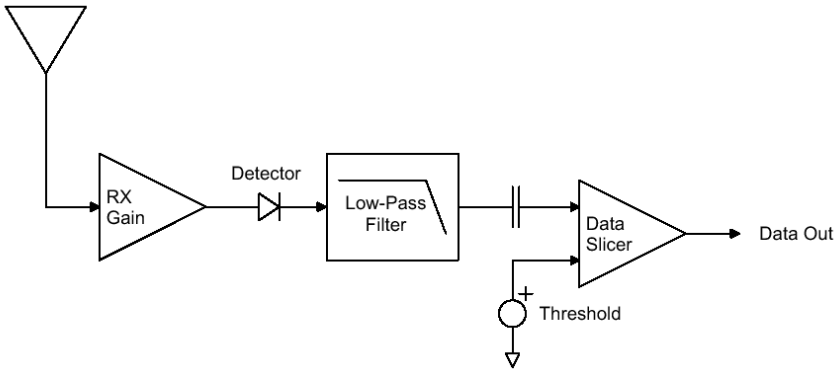


Figure 14: Receiver Signal Processing
(RF Monolithics Inc. 2001)

The threshold provides a squelching action to keep the receiver quiet unless a signal of reasonable significance is detected. Raising the threshold reduces the range, but limits the degree to which the receiver unnecessarily wakes the microcontroller up out of low power sleep mode.

Before any data is sent, a data slicer training pattern of 11001100110011001100 is transmitted at the start of each packet to set the slicer threshold to the halfway point. There are various coding approaches to assuring minimum run length and DC balance during the remaining data transmission. The trade off on using a more time efficient coding scheme is the amount of processing required at each

end (Howell 1998, 33:60-73). Eight bit to ten bit encoding was selected as the most appropriate coding scheme to implement, but some of the other more common coding schemes are also discussed below:

- Manchester Encoding

Manchester encoding is the simplest scheme requiring a minimum of processing complexity. Manchester encoding sends each bit twice, the second copy being inverted. This has a very good maximum run length of only two bits, but halves the effective symbol rate, meaning that it's only 50% efficient.

- Eight Bit to Twelve Bit Encoding

Eight bit to twelve bit encoding maps each of the eight bit patterns into 256 carefully chosen 12 bit patterns out of the available 4096. Maximum run length is 6 and this code is 67% efficient.

- Eight Bit to Ten Bit Encoding - Gigabit Ethernet IEEE 802.3z

IEEE 802.3z Gigabit Ethernet uses a more complicated version of this basic principle. This eight bit to ten bit code patented and licensed from IBM originally for the Fibre Channel standard has a maximum run length of five consecutive 0s or 1s (Franaszek, Peter, and Widmer 1984). The code also has a maximum digital sum variation from -3 to +3. Digital sum variation is a running count of the zeroes and ones, counting a zero as minus one, and a one as plus one. There are extra coded words for link control, and of the 268 codes, 134 are disparity neutral. It works by encoding the first five bits as a six bit group according to a lookup table. The second group of three bits are encoded into a four bit group from one of two tables, the choice of which depends on the running disparity (Franaszek and Widmer 1983, 27:440-451).

This eight bit to ten bit code is also a moderately strong error checking mechanism. This is due to the fact that only certain code groups can be selected at any given time; the choice of which code comes next is partially determined by previously received data.

Although this code sounds as though it would require significant memory and processing requirements, in practice it can be implemented as a finite-state machine in just a few hundred gates. This coding is 80% efficient.

- Scrambling

Scrambling is a technique which has a low overhead and a reasonably low processing requirement. By scrambling the data, it effectively randomises it. Scrambling for the purposes of removing patterns in the source data is termed "data whitening".

One technique is to use a pseudo-random repeating sequence that modifies the data stream through the exclusive-or operator. The same process at the receiver recovers the original data, assuming that the pseudo-random sequence is identical and synchronised. The other main approach uses a linear shift register.

A stream of patterned data — even long strings of zeros or ones — is transformed into what looks like a random bit pattern. The inverse operation at the receiver recovers the original data. There is a minute possibility that data to be coded will end up being scrambled into a long string of ones or a long string of zeros. If that is the case, the transmission fails but it will be encoded differently on the next re-try.

The previous codes guaranteed a short minimum run length and DC balance. The scrambling technique provides a long run approximation to these ideal characteristics in a statistical sense, but short run variation can periodically lead to unacceptable results. The extent to which the short run variation departs from the required channel characteristics is also dependant on the instantaneous transmission range and other factors.

Efficiency is related, but not equal to the scramble key/payload size ratio. Some systems are more efficient because they do not explicitly have to transmit the scrambler key. The Bluetooth standard does not need to transmit a scramble code on each packet transmission due to a synchronised clock in both the master and slaves. The scrambler key is generated from a combination of the master 48 bit

unique ID and the synchronised clock value (Bluetooth SIG 2001).

Packetisation

The packets are now assembled and sent to the transceiver modulation input pin, as follows:

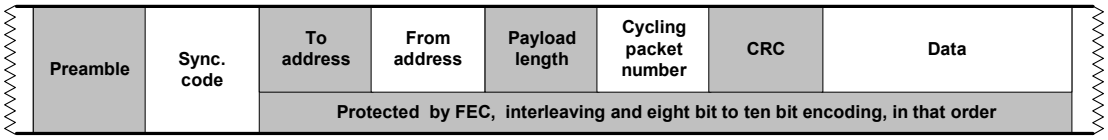


Figure 15: Air Interface Packet Structure

Normally, the preamble is only 2ms long, but when the transmission is from the base station to the DMU, the first packet to be sent is preceded by 800ms of preamble. This 'tickle' wakes up all DMU's in range and keeps them awake in full receive mode. The base station does not require tickling since it is in receive mode whenever it is not actually transmitting.

A "from" address of zero represents the base station. A "to" address of 9 represents a broadcast message to all DMU's.

Bit Synchronisation

The receiver needs to know where the bit boundaries are. This is complicated by the fact there may be up to five bits of the same value in a row. When bits of the same value are sent in a row, there is no transition available to help keep the receiver synchronised. Although both the transmitter and receiver have highly accurate crystal controlled oscillators controlling the timing of the synchronisation algorithm, the problem lies in the fact that there is significant jitter introduced by the transmission and reception process. Even at moderate signal-to-noise ratios, the output of the data slicer will exhibit some jitter in the position of the logic transitions. In addition, random noise spikes can generate false edges at any time.

To counter this, a software phase lock loop is employed. On the receiver side, a timer is configured to overflow with the same period as the basic bit period. If no transition occurs in the expected window, the counter is not affected. If the transition occurs a little before the expected time, the count-up timer value is incremented by 12% of its maximum value. If the transition occurs a little after the expected time, the count-up timer value is retarded by 12% of its maximum value. The assumption is that jitter is a random variable with a mean of zero.

Bit synchronisation is achieved during preamble, ready for the first valid data pattern which is a byte synchronisation pattern.

No end of frame code is required since the message length is given in the packet header. The output from the data slicer is sampled 10 times during the bit period and counts over 5 are considered as ones.

Byte Synchronisation

The byte synchronisation pattern is a reserved 10 bit pattern from the 8 bit to 10 bit encoding scheme that does not occur anywhere in the actual data stream. During the preamble phase, each new incoming bit is left shifted into a register and the old one discarded. At the end of every bit period, the register is checked to see if it is the synchronisation pattern. If it is the right pattern, bit and byte synchronisation has been achieved.

Automatic Repeat Request

Some communication protocols use a version of Automatic Repeat reQuest (ARQ) to ensure that the message gets through if not correctly received on the first try. (This can only be implemented in systems with a back channel.) The receiver may be out of range or find some unrecoverable errors in the data. If the transmitter does not receive an acknowledgment from the receiver within a certain amount of time, it re-sends the information a few more times before giving up. Many elaborate variations on this theme have been implemented to make the best out of the given channel characteristics.

In the protocol designed for the DMU, the ARQ process was not implemented due

to time constraints. This means that the cycling packet number in the packet header is redundant, but it can be used if automatic request repeat is added in the future. There is still an acknowledgement from the receiver which can be checked by the user to see if a command was successfully received, but the transmitter does not check for the absence of this to resend automatically.

Actual Implementation of Channel Encoding

Due to time constraints, only a simplified form of the entire channel encoding process was implemented. This resulted in a reduced but acceptable range of up to 60 metres outdoors.

For a given range, the more palatable bit patterns and greater redundancy for error detection would have increased the probability that decoded packets arrived in an error free (or at least recoverable) state. The coding gain introduced by a particular channel encoding scheme is equal to the extra signal to noise ratio that would be required to provide the same raw bit error probability using the uncoded pattern at a given range.

The more sophisticated channel encoding scheme would have introduced a greater coding gain, and hence range.

3.7.5 LED Status Indicator

As well as the wireless link, there is also a Light Emitting Diode (LED) that can flash in one of three colours. This LED (D101 in Figure 52 on page 181) actually consists of one green LED and one red LED, but if they are both on, it appears orange. This is used as an indicator to convey one-way status communication without the need for a base station. The LED indicates as follows:

- On power up reset, the light goes orange, then rapidly blinks red while the power-on message transmits, then flashes alternately red and green a few times. At the end of the red/green flashing, the internal clock is zeroed.
- At the end of every minute, a very short green flash (30ms) means the internal clock has ticked over another minute. If the flash is longer

(600ms), this indicates that a result set is being recorded for data logging.

- When receiving data, the light is steady green.
- When transmitting data, the light rapidly flashes red.
- If the light is rapidly flashing orange on and off, the batteries have run out and the DMU is continually resetting itself.

3.7.6 Wired Communication Port

If the transceiver fails, wires can be soldered onto the DMU to download any important data that might be otherwise inaccessible.

3.7.7 Programming and Debugging Port

Setting the Program/Run switch to "program" and pressing reset allows the DMU software to be upgraded over the programming serial port. Setting the Program/Run switch to "run" and pressing reset executes the downloaded program. The same port outputs debugging statements if the debug option has been defined during conditional compilation. The emulator also uses this port, so if the emulator is resident, the debug statements are sent to the wired comms port instead.

As a space and power saving measure, no RS232 level conversion is performed on the DMU. A special programming cable contains the level conversion IC which is powered from the DMU when connected to it. The DMU programming cable schematic is given in Figure 54 on page 183.

3.7.8 Message Handling

Incoming messages from the transceiver are fed into a finite state machine. Valid messages are passed to the message handling routine which calls the appropriate functions on behalf of the message. The first task for any message is to reply to the base station with text to let the user know what command has been received and what action will be carried out.

A help screen is available from the base station and is presented here to show the available commands.

Table 4: Base Station Help Screen

```
                                                                  (__)
                                                            \     (oo)
_____________________________________________________        >------\/
             UDDER Base Station                            ->*_____,)
                                                             /| ~  |\
  Ver 1.00         (c) 2001, InterAg Ltd.                   ` "    " `
_____________________________________________________________________
_____________________________________________________________________
/: output >        Format is   "=[command][sub-command][from ID][to ID];"
/: output >        E.g.  [it05]     or type  [?  for help.
/: input? > [?

============================================================
            Help on Communication Message Format
============================================================
Format is   "[ command  sub-command  from_ID  to_ID]"
where items in the brackets are represented by a single letter.
Always start the command with a '['
Always end the command with a ']'
In between comes the command and sub-command letters,
followed by the 'from' ID number, followed by the 'to'
ID number.  A 'to' ID of 9 commands all DMU's at once.
A 'from' ID of 0 indicates the base station.
The case of the letters is not important.
If there is no sub-command, any letter will do.
Example 1: [bb03]  means request a verbose summary from
                   DMU ID 3 and reply on both the radio and
                   wired comms link.
Example 2: [dt01]  means request to download all result sets
                   from DMU ID 1 replying on the radio link
                   only.

=====================================================================
                           Command Table
==================================+==================================
            Command               |          Sub-Command
==================================+==================================
test                          [t] | none: any letter will do
transmit ID                   [e] |
wake up                       [w] |
----------------------------------+----------------------------------
download all result sets      [d] | reply on radio           [t]
snap shot CSV                 [s] | reply on wired comm port [c]
summary verbose               [b] | reply on both            [b]
setup info verbose            [i] |
flash LED                     [f] |
roll call                     [r] |
----------------------------------+----------------------------------
gascell override              [o] | make active              [a]
start delivery override       [q] | make inactive            [i]
----------------------------------+----------------------------------
gascell override value        [p] | off if override active   [f]
start delivery override value [z] | on if override active    [n]
----------------------------------+----------------------------------
restart delivery              [j] | confirm                  [k]
=====================================================================


/: input? >
```

Command Set

The commands can reply on the wired comm port, the wireless link, or both. The method of reply is specified by the sub-command where appropriate.

If the message has a "to" ID of 9, it is a broadcast message and all DMU's respond. A broadcast message means the DMU's respond after a delay determined by their ID number. This is to ensure that they do not all try and reply at once.

The following commands are available.

- Snapshot Command

The snapshot command allows for a snapshot of the state of the device and the current readings from the environmental sensors. It is the same as a result set taken during data logging, but is transmitted instead of being stored. An example of the user requesting a snapshot is given in Table 6 on page 112.

- Download Command

The download command transfers the entire data log to the base station.

- Setup Information Command

A setup command responds with all calibration figures, threshold settings, safety limits and time constants stored in the device during program download. Table 9 in Appendix A (page 175) shows the user requesting setup information.

- Wake Up Command

The wake-up command keeps the DMU awake for 10 seconds instead of the usual 2.5 seconds. This is useful for bench testing the digital board without a transceiver board fitted.

- ID Command

When this command is received, it updates the cow proximity array for the current result set. The relevant bit is set according to the "from" address of the received packet. This is the mechanism by which the individual proximity of nearby cows are logged for each recording period.

- Gascell Override Commands

The gascell switch can be controlled by the "gascell override value" command if external control has been obtained through the "gascell override" command. This is subject to the safety limit checks specified on page 57.

- Start Delivery Override Commands

The start of delivery can be forced by the "start delivery override value" command if external control has been obtained through the "start delivery override" command.

- Restart Delivery Command

The delivery programme can be reset to the beginning of the delivery profile.

3.8 Executive Control

All control and decision based processing occurs on-board the DMU. This allows for autonomous control of each DMU in a distributed network of intelligent delivery and sensing devices. This is an absolute requirement since communication with the base station is intermittent.

3.8.1 M16C Microcontroller

To provide the intelligence and memory for the DMU, the M30624FGLGP from the M16C family of Mitsubishi microcontrollers was chosen. This is U101 in Figure 50 on page 179. This represented the most capable microcontroller that

could be found, given the small amount of space available for the electronics and the limited budget for development tools.

Highlights of the microcontroller are:

- 16 bit architecture designed specifically around efficient execution of C code.
- 4 stage pipeline.
- Special low noise IO pin hardware design and packaging for high ElectroMagnetic Interference (EMI) acceptance and low EMI emissions.
- Low power:
    - 2μA in sleep mode with 32kHz sub-clock operating timers.
    - 40μA executing code with 32kHz sub-clock.
    - 7mA executing code at 10MHz, divide by 1, no-wait state bus.
- 10MHz operation down to 2.7V
- 256K flash memory which is in-system and self re-programmable.
- 20K Random Access Memory (RAM).
- 14x14mm Low profile Quad Flat Pack (LQFP) 100 pin package with 0.5mm lead pitch.

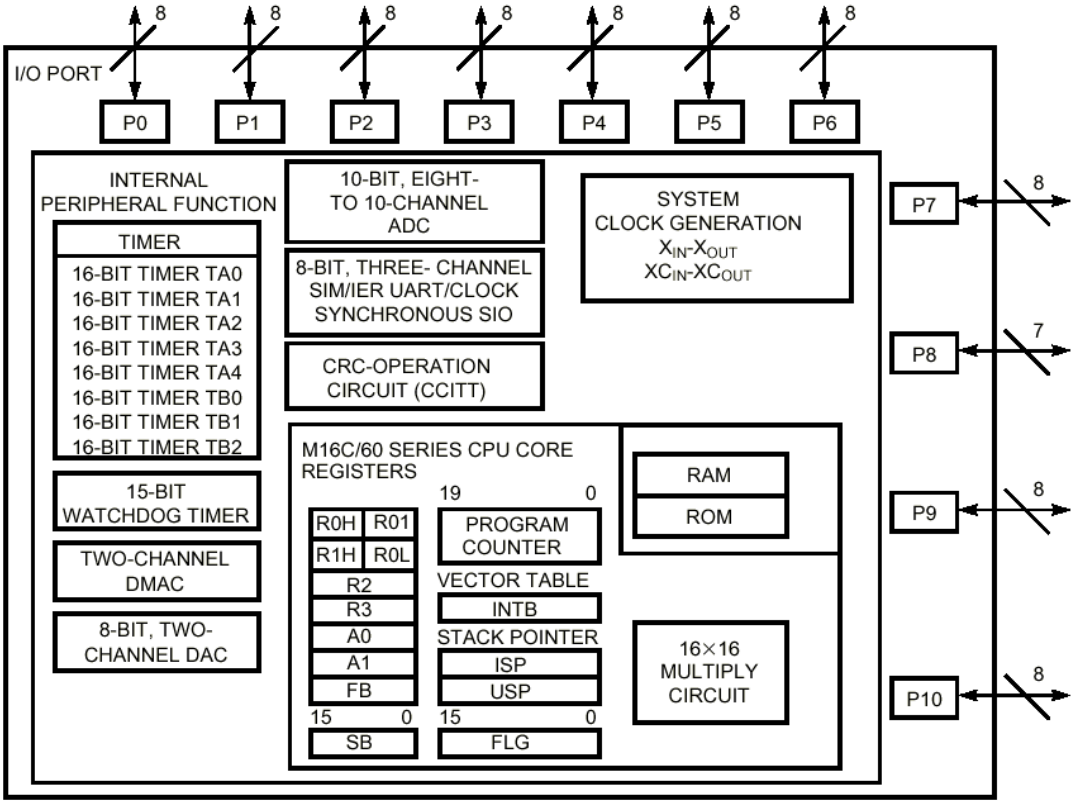


Figure 16: Mitsubishi M16 Microcontroller Block Diagram
(Mitsubishi Electric Corporation 2001)

3.8.2 Real Time Clock

A timer runs off the 32kHz sub-clock which is permanently on. It generates an interrupt exactly once a minute to update the real time clock counter.

3.8.3 Unique ID

The gascell monitor integrated circuit (U102 in Figure 52 on page 181) has a unique code 64 bits long. This is lasered onto the IC at the factory and guarantees that every DMU ID will be unique. The first 8 bits are a manufacturer family code. The next 48 bits the unique serial number. The last 8 bits are a CRC of the first 56 bits.

3.8.4 Data Logging and Retrieval

Every 15 minutes, a full set of measurements is taken and stored. The measurements taken are given in Table 5.

Table 5: Logged Data Result Set

Delivery Profile Management	▪ Profile Estimates	- Gascell Actual Integrated Current [mAHr] - Estimated Volume Delivered [mL]
	▪ Profile Targets	- Gascell Target Integrated Current [mAHr] - Target Volume [mL]
	▪ Gascell Instantaneous Readings	- Gascell Voltage [V] - Gascell Peak Current [mA]
	▪ Gascell Load Control Flags	- Gascell Switch - Gascell Override - Gascell Override Value
Sensor Data	▪ Light Intensity [%] ▪ Temperature From Gascell Monitor [deg. C] ▪ Temperature From Pressure Sensor [deg. C] ▪ Pressure [mbar] ▪ Motion Cycles [cycles] ▪ Motion % Open [%]	
Cow Proximity Flags	▪ Cow Number 1 Proximity ▪ Cow Number 2 Proximity ▪ Cow Number 3 Proximity ▪ Cow Number 4 Proximity ▪ Anonymous Cow Proximity	
Self Diagnostics	▪ Power Supply	- Battery Voltage [V] - Battery Current [mA] - Vdd [V] - AVdd = Vref [V]
	▪ Status Flags	- Voltage Regulator Unregulated - Voltage Regulator Shutdown - Any Reset - Power Fail Reset - Watch Dog Reset

Judicious use of bit packing and a simple form of memory compression enable the storage of these items into 20 bytes of memory. This allows 720 data sets (7 days worth of data) to be stored before the data begins to be overwritten,

starting with the oldest record. This allows indefinite, uninterrupted data logging, as long as a download is accomplished once a week.

At any time, a snapshot can be requested manually over the wireless link. In that case, a full set of measurements is immediately taken and the results transmitted. The measuring process takes 0.6 seconds, allowing manual capture of data to be observed at a much higher rate than the datalogging frequency.

3.8.5 Event Scheduler

The event scheduler is driven from the real time clock tick. For example, on every 5^{th} tick, it calls the gascell switch decision routine, on every 15^{th} tick it calls the data logging routine to measure and store the next set of results. Other events are handled in the same way: Current analogue to digital converter calibration, TC1073 voltage regulator enable and ID transmission.

3.9 Environmental Monitoring

3.9.1 Temperature Sensor

Given that vaginal temperature has proven to be such an important physiological factor, a temperature sensor has been included in the DMU.

In fact, there are two independent sources of temperature measurement available from opposite sides of the digital board. Accuracy is 0.1°C for both.

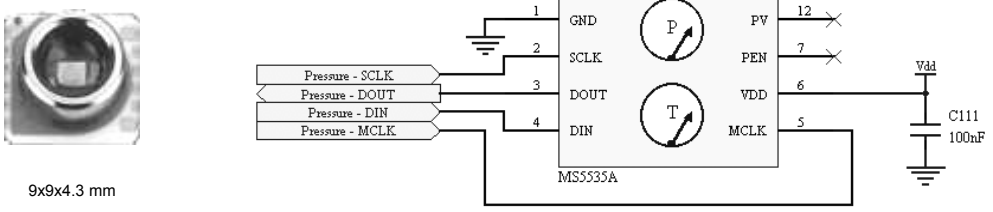
One source comes from the gascell monitor IC and the other from the pressure sensor IC. The gascell monitor IC temperature sensor (U102 in Figure 52 on page 181) is of the digital IC type, relying on the difference in frequency between two oscillators. One oscillator is designed to be sensitive to temperature variation and one not. The difference in frequency is converted to a digital form and stored in a register for subsequent access when requested. The temperature sensor on the pressure sensor IC is described later.

3.9.2 Pressure Sensor

Since the syringe relies on differential pressure across the piston to deliver the drug, the ability to obtain pressure readings helps in understanding the experimental system. In fact, only internal syringe pressure is measured. No account is made of fluctuations in ambient external pressure which have the potential to affect the delivery rate slightly.

The MS5535 is a 0 to 14 bar pressure sensor from Intersema, Switzerland and is represented in the schematics as U104. Figure 17 shows the schematic symbol by itself. The readings are requested and obtained by the microcontroller over a proprietary four-wire synchronous serial interface. A temperature sensor is provided in the same module for temperature compensation. The MS5535 was chosen for its low power operation, small size, large pressure range, adequate accuracy and high resolution output. It was designed for diving computer watches and tyre pressure gauges.

The 0 to 2 bar version is used in altimeters and can register a change in atmospheric pressure when moved through a vertical height of only one metre. The MS5535 has a pressure resolution of 1.2mbar, and a temperature resolution of 0.015°C.



Physical DMU Schematic

Figure 17: Pressure/Temperature Sensor Physical and Schematic

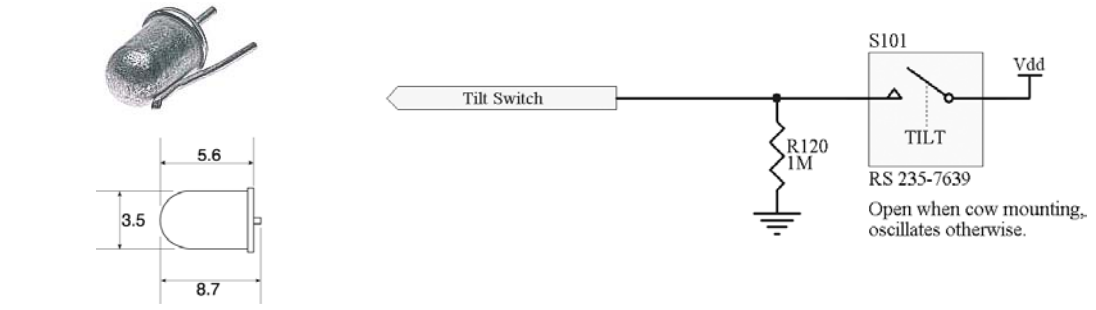
The piezoresistive pressure sensor is a Micro Electro-Mechanical Systems (MEMS) device. MEMS are chip-level devices that can either sense or control the physical environment. They are commonly made out of silicon with moving

parts constructed by micromachining processes. MEMS use a number of manufacturing steps derived from integrated circuit fabrication techniques.

The on-chip 15 bit analogue to digital converter is used for both pressure and temperature readings. The module is calibrated at two temperatures and pressures at the factory for determining the six calibration coefficients. These are read and used by the software running on the microcontroller to correct for both the gain and offset errors of the pressure sensor, temperature sensor and analogue to digital converter. Second order compensation is used to get the most accuracy for temperature conversion.

3.9.3 Motion Sensor

There is no literature on motion sensors being located in the vagina, but commercially available sensors described in the introduction use pedometers placed on legs and collars.



Physical Dimensions in mm (RS Components Ltd. 2000) | DMU Schematic

Figure 18: Motion Sensor Physical and Schematic

The most sophisticated of the commercial motion detectors utilise a MEMS multi-axis accelerometer. The motion detector used on the DMU is much simpler, consisting of a ball-in-cage tilt switch: S101 in Figure 18. There are two contacts that form the sides of the cage; if the ball touches both sides of the cage, the switch is closed and the input to the microcontroller goes high. The input lines to the microcontroller are configured as standard input pins with no internal pull-up resistor. The full schematic is presented in Appendix B: DMU Schematics.

Being a non-mercury mechanism it is completely safe for use inside the cow. The tilt switch oscillates when the cow is level and moving, staying open circuit when the cow is inclined head up. In retrospect, mounting the switch so it would be closed when the cow is inclined head up would have been more useful because a head up inclination may indicate estrus mounting behaviour. However, a head up inclination of the device could also be simply due to the fact the cow is lying down at that angle. Sloping pastures could also present a problem.

The maximum angle differential between open and closed is 15 degrees. Although nowhere near as sophisticated as commercial devices based on MEMS accelerometers, the hope was that it would be good enough for basic motion detection to assess activity level, and mounting activity of the riding cow.

The switch is positioned with its long axis co-incident with the long axis of the syringe which means that its behaviour would be the same irrespective of the rotation of the DMU within the cow.

Two different values are read at the end of each data logging period: "motion cycles" and "motion percent closed".

- Motion-cycles are the number times the switch contacts have been made and then broken, giving an estimate of overall cow activity in the same way that pedometers fitted to the legs or collars of cows have been proven to do. The intention is to provide an indication of overall activity. This is accomplished by establishing the tilt switch signal as a count source for a counter on the microcontroller.

- Motion-percent-closed is the percentage of time that the ball has stayed in contact with the cage contacts. The intention is to provide an indication of mounting behaviour. This is accomplished by establishing the tilt switch as a gate signal for a counter on the microcontroller. The free running 32.768kHz oscillator is on even when the microcontroller is in sleep mode for the purposes of maintaining the real-time clock. This oscillator also provides the count source for the motion-percent-closed counter, only decrementing the counter when the gate is closed.

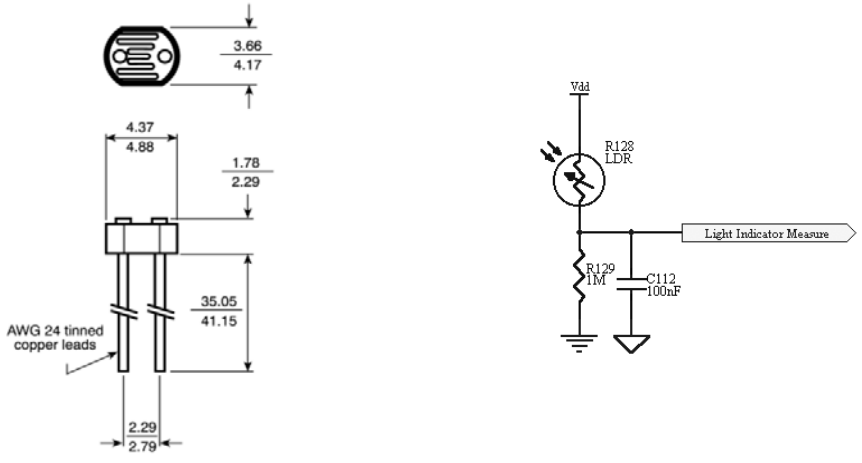
The quality of information is not expected to stand alone in determining estrus, but to act as an indicator in conjunction with other systems to increase accuracy of detection.

The data obtained could be processed in a number of ways. In the introduction, it was reported that cows in heat typically walk two to five times more than when they are not in heat (Nebel and Walker 1998). The Afikim pedometer system takes the rolling average over the last ten days and compares it to the present day. A 70% increase over the 10 day rolling average is thought to be a reasonable indicator of increased activity due to estrus, but even then, the results need interpretation on a cow by cow basis. Further interpretation is required if the pedometer counter values are not read at regular intervals, but at variable times throughout the day, as with robotic milking attendance.

Results comparing pedometer data with observed behavioural patterns are good for barn housed animals, but less so for pasture based animals.

3.9.4 Light Sensor

A Light Dependant Resistor (LDR) provides an uncalibrated light intensity function.



Physical Dimensions in mm (RS Components Ltd. 2000)	DMU Schematic

Figure 19: Light Sensor Physical and Schematic

The LDR (R128 in Figure 19) may be useful in determining the status of the device. For example, if the temperature decreases markedly, this might be interpreted as a severe drop in body temperature of the animal. If it corresponds with a sudden increase in light level however, one might conclude that the device simply protruded from the vulva for a while. The light intensity reading has a resolution high enough to determine protrusion even at night.

The light dependant resistor is mounted in close proximity to the LED. This allows for self testing. A light reading can be taken with the LED on, and again with it off to give confidence that the light dependant resistor is operating correctly.

3.9.5 Cow Proximity

Since the DMU in each cow has the ability to both transmit and receive, the cows have the ability to communicate with one another over a short range (30m).

Current behavioural recording systems such as tail-paint, MountCount and HeatWatch rely on the physical interaction between cows in heat, i.e. contact during mounting behaviour. They miss cows that prefer to associate with others in estrus, but who prefer not to be mounted themselves. With a short range inter-cow communication system, it is possible to record the grouping of animals throughout the day. This will detect all types of grouping behaviour including cows that prefer not to be mounted while in estrus.

More subtle behavioural patterns can be established by combining the data from the other on-board sensors with the grouping data. For example, if a cow does not have an increase in vaginal temperature, but begins socialising with the group of cows which are in heat, and participating in mounting behaviour, this would allow a study to target cows of that nature.

The absolute position of the animals cannot be determined from the data set, nor is any individual data element a reliable indication of the range between animals involved in a data exchange. However, by analysing enough exchanges over time, an accurate statistical representation of animal grouping will be discerned over a time period of several hours.

The inter-cow communication function is quite rudimentary: Every half hour, each cow transmits it own ID number. If any other cows are in range, they will record the fact that a reception from that particular cow has been received. At the end of the data logging period, a flag will have been set for all cow IDs that have been heard from in that period. The cow proximity flags are stored as part of the current result set before being cleared for the next data logging period.

3.10 Software Design Methodology

The source code for the base station and DMU is common, being written almost entirely in the C programming language. Assembly was used sparingly where C was not suitable. To generate the executable for the base station instead of the DMU, conditional compilation is used. This aids in software development and maintenance due to the fact that there are many common software routines. The use of code libraries encouraged structured software development and reduced compilation time considerably.

The M21 Real Time Operating System (RTOS) was obtained from M2 Technology in Auckland, New Zealand. The use of this product would have made programming the DMU and base station much easier since it has networking capability built in. Unfortunately, the conditions of use specified that it could only be applied to a non-commercial project. Once it became clear that the DMU would be further developed beyond the scope of this thesis, the M21 RTOS was removed from the project. As a result, more work had to be put into the low-level coding of communications routines. The extra time devoted to this meant reduced messaging capability and sophistication.

Object oriented methodology was applied to the software design process. The C language by itself does not directly support object oriented programming, but with discipline, the software engineer can organise the code in an approximate manner. Applying scope rules and access modifiers appropriately can encapsulate variables and functions, effectively turning them into member variables and methods.

A layered approach to the software design decouples the low level driver routines for peripherals from the specific use required by the application. At the lowest level, there is a driver routine for each individual hardware device which, when put together, form the Basic Input/Output System (BIOS). For the more complex peripherals, including the transceiver and the gascell monitor, a middle layer provides a range of standard objects with which any general purpose application can interact with. On top is the application layer that talks only to the layer immediately below itself. Only the top layer is application specific. This allows for greatest portability, maintainability and re-use of the software source code.

Taking the transceiver as an example, the BIOS routines for mode control, preamble generation, receiver interrupt processing, noise spike rejection, and initialisation of the device configure port pins in the appropriate time sequenced manner. Above this, the middle layer provides higher, general purpose, functions such as transmitting an array of byte values. This involves the anti-collision algorithm, transmit mode setting, preamble generation and transmission of bytes using the BIOS routines.

The top level can then interact with this Application Programming Interface (API) at a higher level. That is, the application layer can deal with the relatively abstract concepts of sending and receiving messages, rather than having to worry about the state of individual port pins, or even which medium it is transmitting on (wired, wireless or both).

3.11 Base Station

The purpose of the base station is to relay commands typed into the laptop for transmission over the wireless link. As shown in Figure 20, the commands are parsed and sent to the transceiver over the RS232 serial cable at 57,600 Baud. DMU reply packets are captured by the base station transceiver and reformatted for serial transmission over cable in the reverse direction to the laptop. The wired link is duplex, the transceiver link is half-duplex at 23k Bits Per Second (BPS).

The base station hardware is similar to the DMU. It consists of the same components and schematic, minus the DMU peripherals, and with the addition of some dedicated RS232 level conversion.

In fact, the development DMU board becomes the base station simply by downloading the base station software which ignores the extra peripherals. This development board is documented more fully in Appendix E starting on page 199.

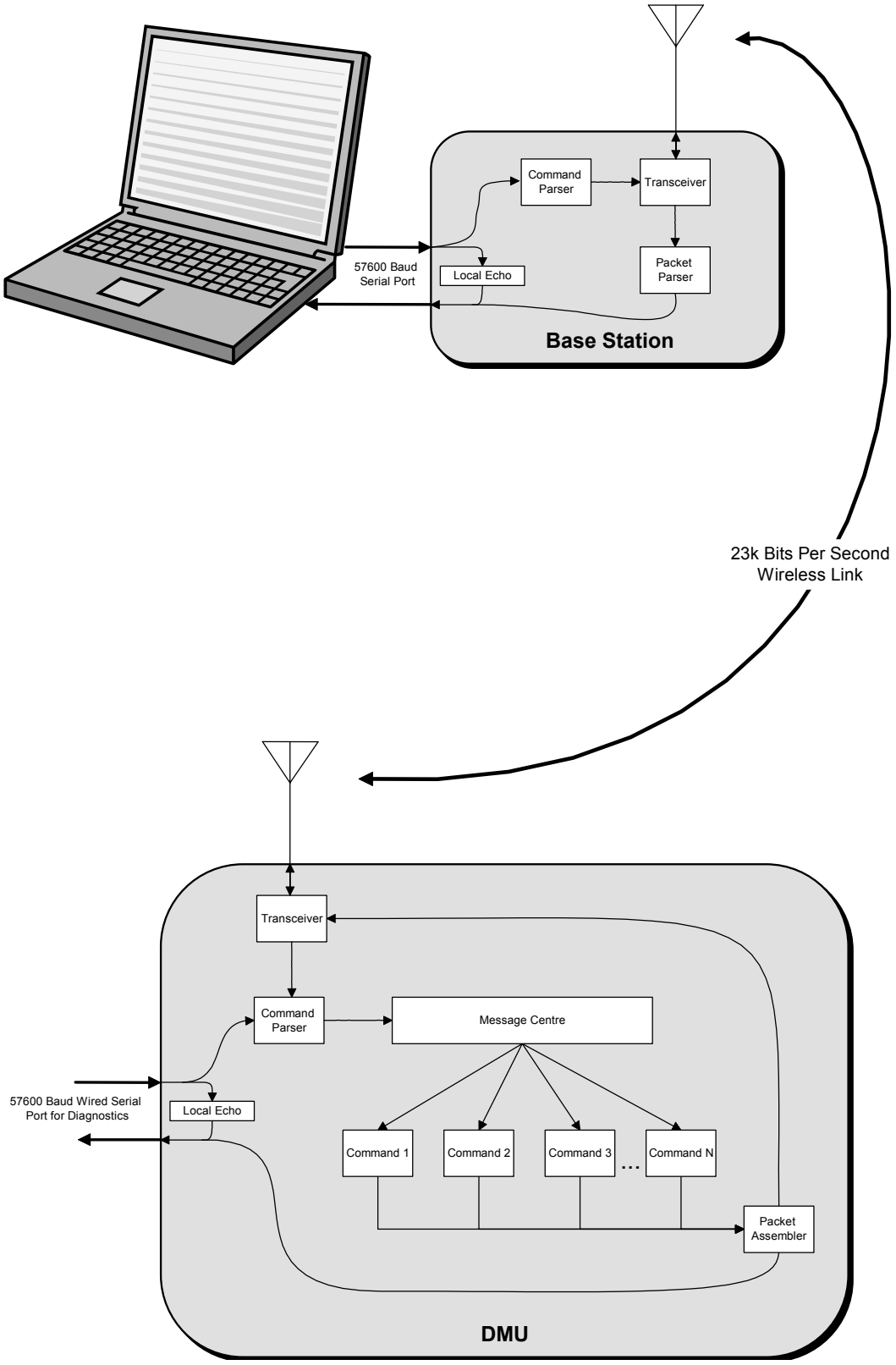


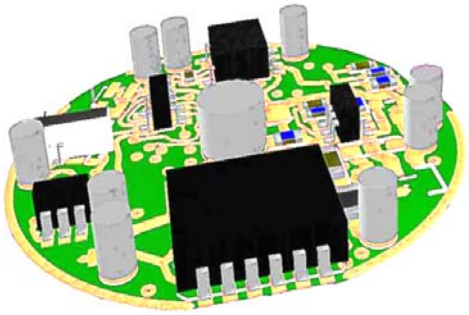
Figure 20: Base Station/DMU Communication Flow

3.12 Construction

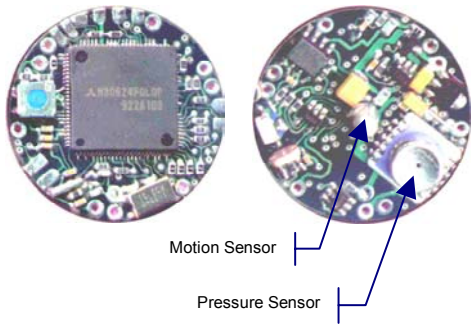
The hardware and software design is standard, but the difficulty lies in finding a combination of devices that fit the special needs of this application. These devices have to be compatible in terms of

- Small physical size.
- Low power operation.
- Obtainable in sample quantities.
- Evaluations kits and development tools priced within tight budget.
- Electromagnetically compatible with the transceiver in close proximity.

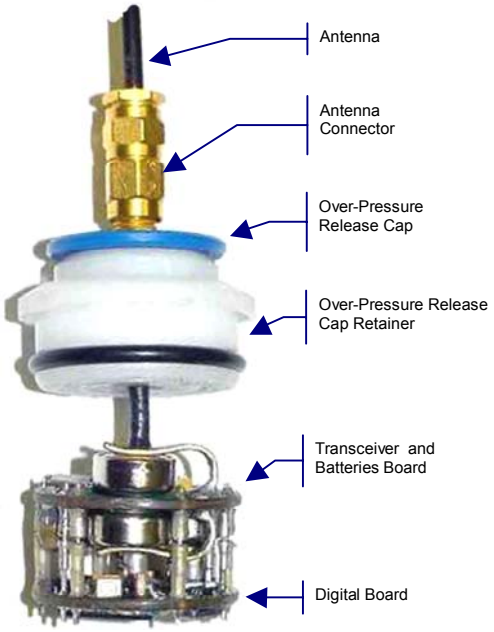
Layout is crucial to the success of the transceiver operation. Normally, microcontrollers are not used in close proximity to radio frequency components. The spurious signals coupled from the microcontroller clocking elements into the radio circuits can affect both transmission and reception. To mitigate this, the transceiver and microcontroller are placed at opposite ends of the device. Attention to power supply distribution and other design rules allows a successful arrangement of components. The six layer PCB has dedicated power and ground planes on each board, which along with other techniques, means bulky shielding is unnecessary. As a result, the electronics package, including batteries and gascell fit into a cylinder 2.8cm in diameter and 2.5cm in length. Four copies of the DMU exist.



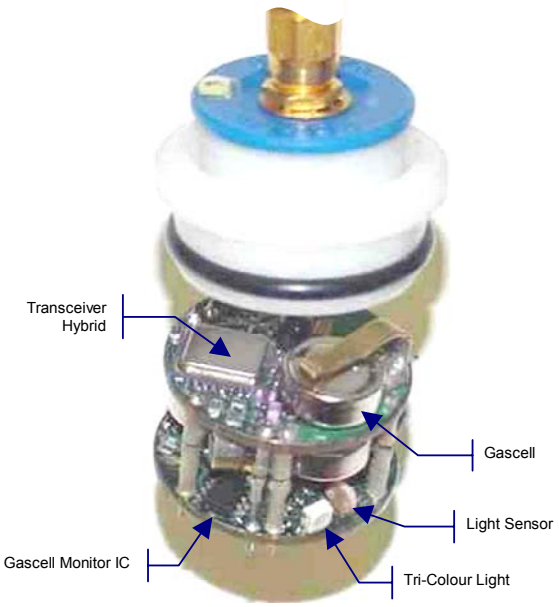
3D PCB CAD Model of Side 2 of Digital Board for Visualisation of Fit



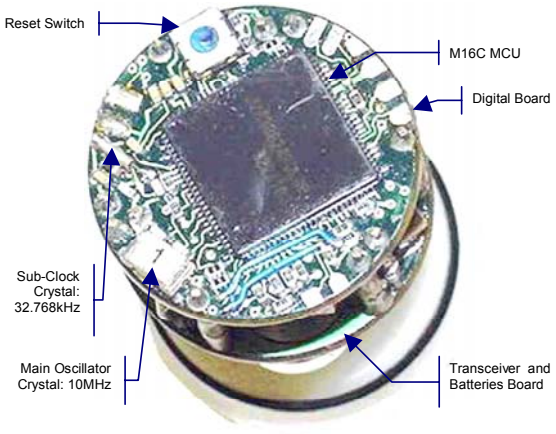
Sides 1 and 2 of Digital Board
Shown Actual Size: 28.6mm Diameter



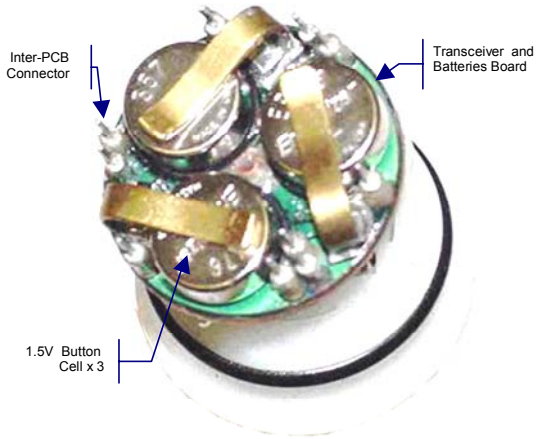
Electronics Package – side on



Electronics Package from Antenna End



Electronics Package from Microcontroller End



Electronics Package from Microcontroller End with Digital Board Removed

Figure 21: DMU Electronics Construction

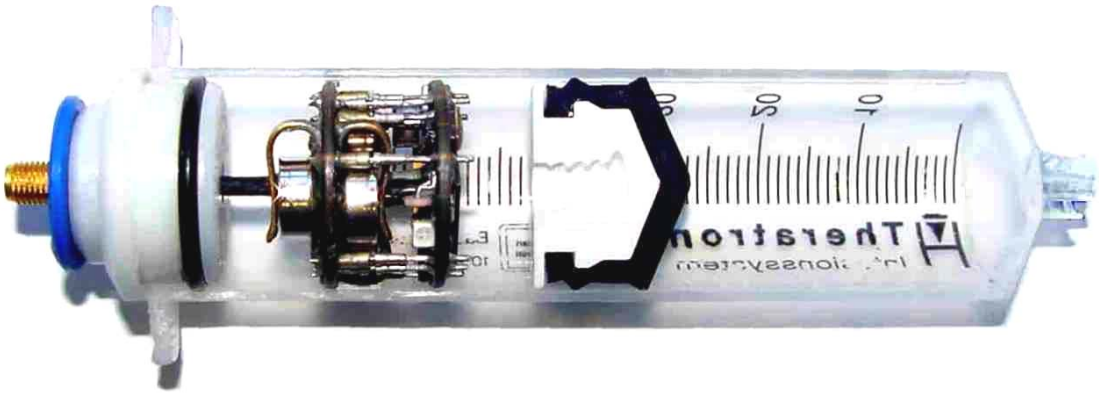


Figure 22: DMU Electronics Package Fitted to Modified Theratron© Syringe, Sectioned for Display and Shown Actual Size

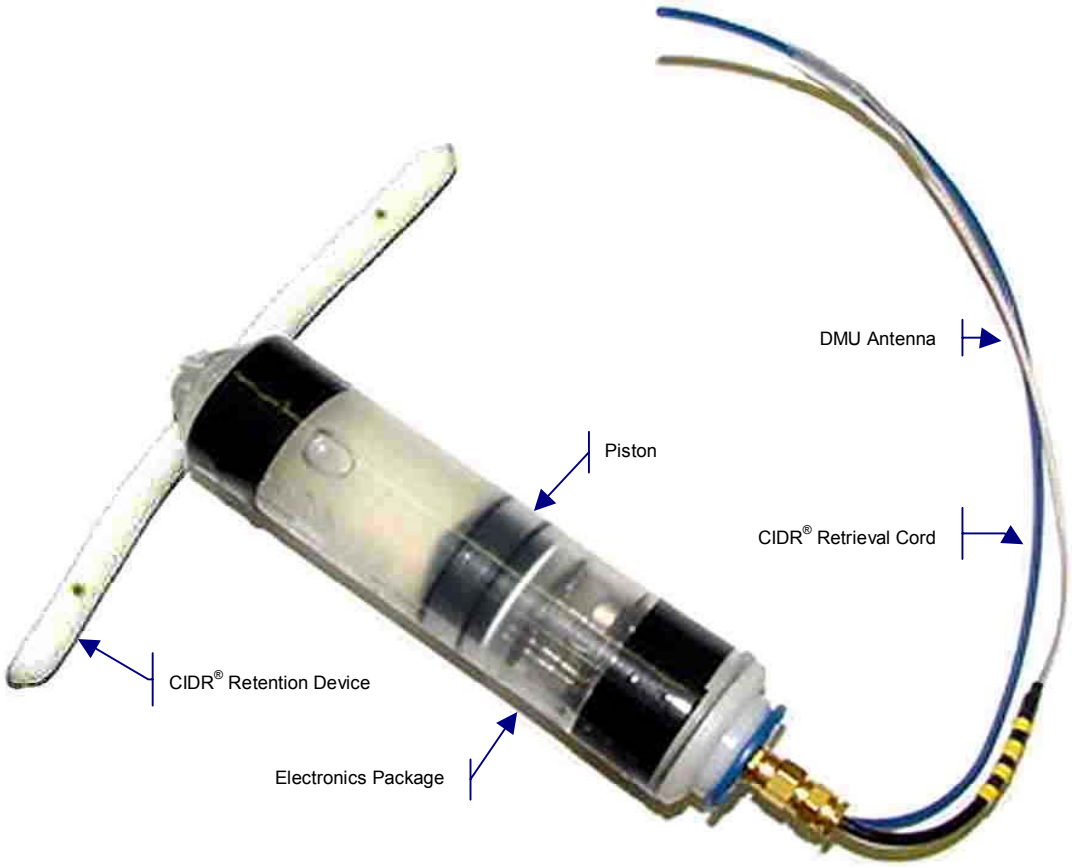


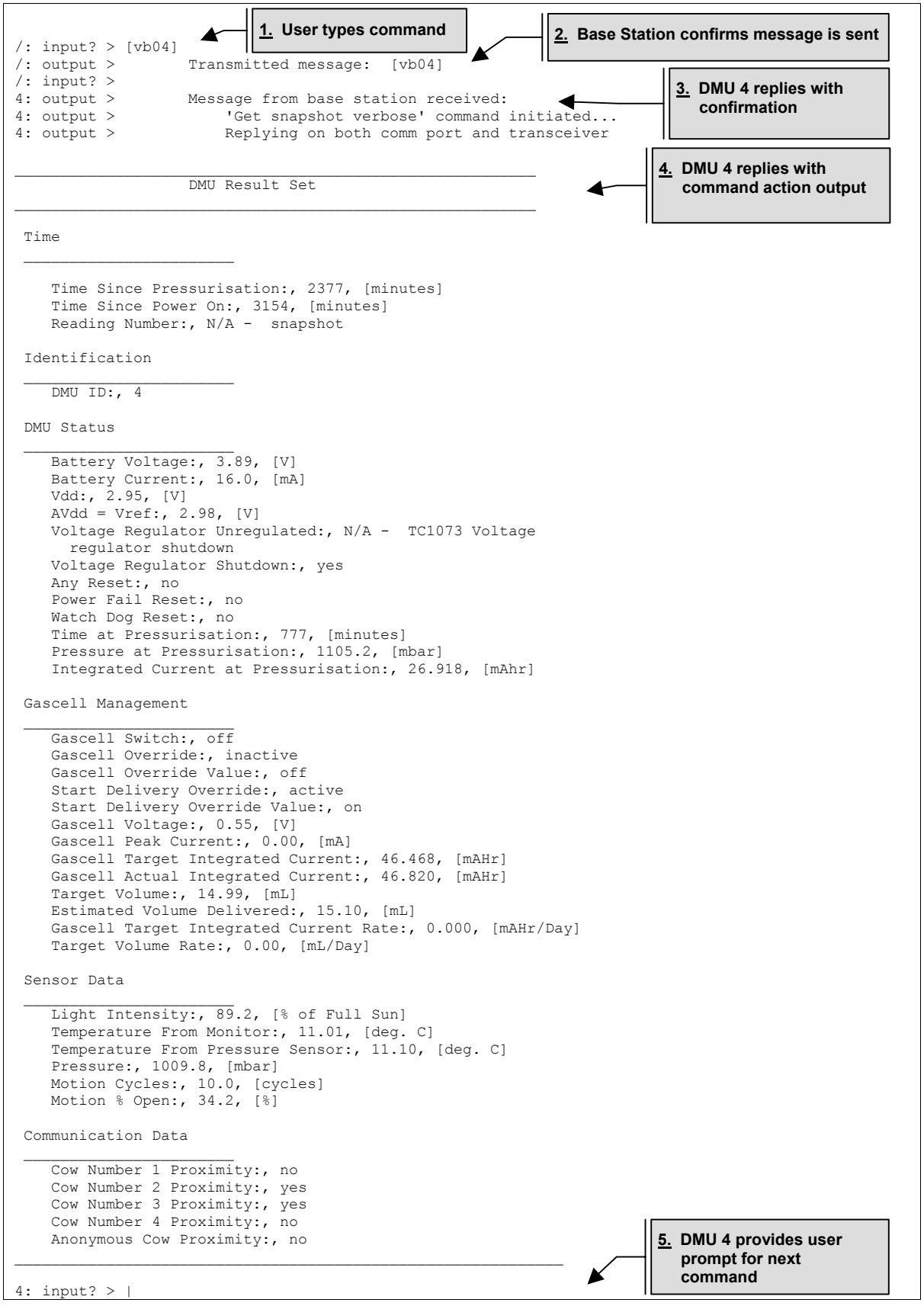
Figure 23: Complete DMU Ready for Deployment

3.13 Bench Testing

3.13.1 Communication and Measurement Testing

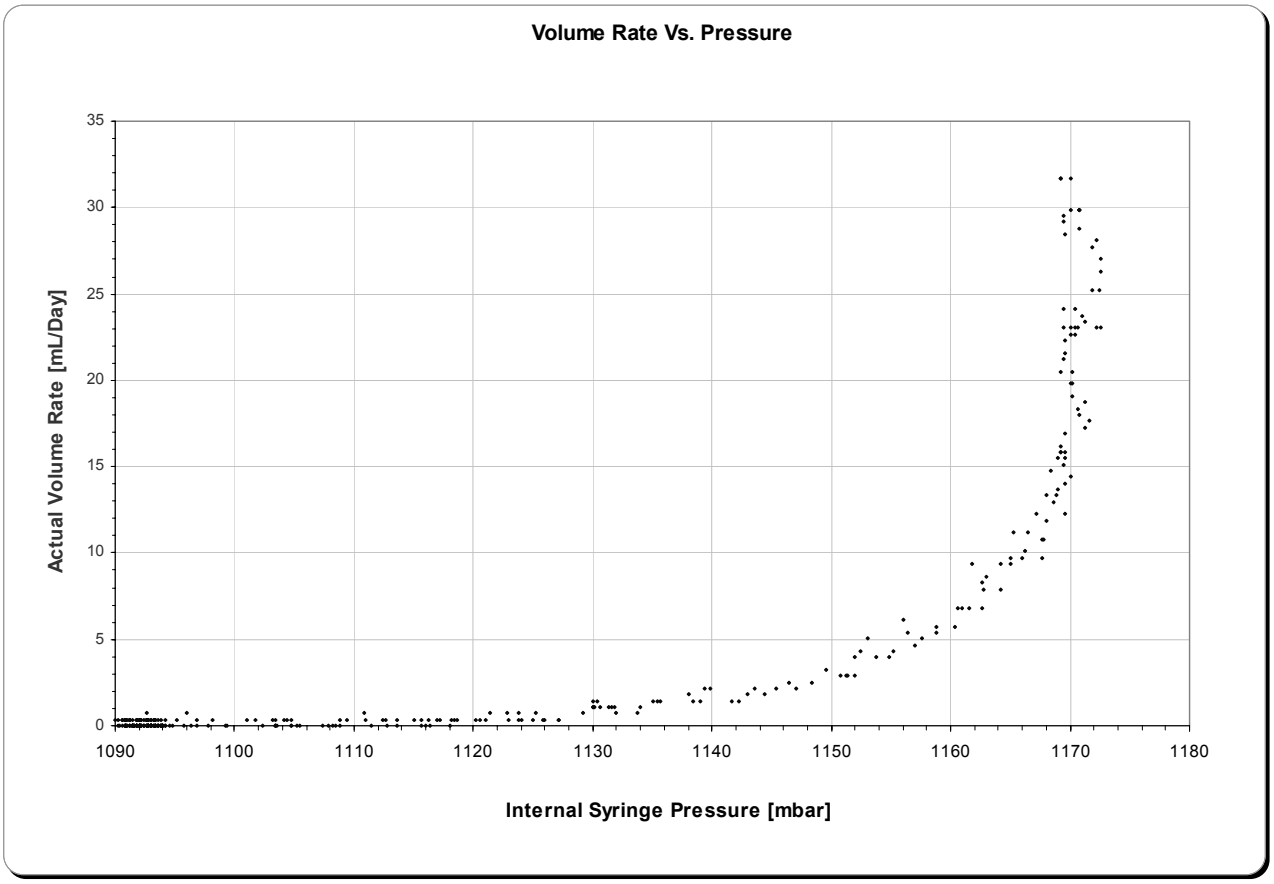
Several results from bench testing are presented. The first is an interaction between the user and a DMU showing a command typed into the laptop by the user. Once the command has been parsed and found to be valid, the base station sends it, informing the user of the transmission. The DMU replies with confirmation that it has received the command and then carries it out.

Table 6: User Requesting a Snapshot From DMU 4 Over Wireless Link


1. User types command
2. Base Station confirms message is sent
3. DMU 4 replies with confirmation
4. DMU 4 replies with command action output
5. DMU 4 provides user prompt for next command

```
/: input? > [vb04]
/: output >        Transmitted message:  [vb04]
/: input? >
4: output >        Message from base station received:
4: output >            'Get snapshot verbose' command initiated...
4: output >            Replying on both comm port and transceiver

_____________________________________________________________
                    DMU Result Set
_____________________________________________________________

Time
 _________________________

    Time Since Pressurisation:, 2377, [minutes]
    Time Since Power On:, 3154, [minutes]
    Reading Number:, N/A -  snapshot

 Identification
 _________________________
    DMU ID:, 4

 DMU Status
 _________________________
    Battery Voltage:, 3.89, [V]
    Battery Current:, 16.0, [mA]
    Vdd:, 2.95, [V]
    AVdd = Vref:, 2.98, [V]
    Voltage Regulator Unregulated:, N/A -  TC1073 Voltage
      regulator shutdown
    Voltage Regulator Shutdown:, yes
    Any Reset:, no
    Power Fail Reset:, no
    Watch Dog Reset:, no
    Time at Pressurisation:, 777, [minutes]
    Pressure at Pressurisation:, 1105.2, [mbar]
    Integrated Current at Pressurisation:, 26.918, [mAhr]

 Gascell Management
 _________________________
    Gascell Switch:, off
    Gascell Override:, inactive
    Gascell Override Value:, off
    Start Delivery Override:, active
    Start Delivery Override Value:, on
    Gascell Voltage:, 0.55, [V]
    Gascell Peak Current:, 0.00, [mA]
    Gascell Target Integrated Current:, 46.468, [mAHr]
    Gascell Actual Integrated Current:, 46.820, [mAHr]
    Target Volume:, 14.99, [mL]
    Estimated Volume Delivered:, 15.10, [mL]
    Gascell Target Integrated Current Rate:, 0.000, [mAHr/Day]
    Target Volume Rate:, 0.00, [mL/Day]

 Sensor Data
 _________________________
    Light Intensity:, 89.2, [% of Full Sun]
    Temperature From Monitor:, 11.01, [deg. C]
    Temperature From Pressure Sensor:, 11.10, [deg. C]
    Pressure:, 1009.8, [mbar]
    Motion Cycles:, 10.0, [cycles]
    Motion % Open:, 34.2, [%]

 Communication Data
 _________________________
    Cow Number 1 Proximity:, no
    Cow Number 2 Proximity:, yes
    Cow Number 3 Proximity:, yes
    Cow Number 4 Proximity:, no
    Anonymous Cow Proximity:, no
_____________________________________________________________

4: input? > |
```

3.13.2 Variable Rate Delivery Testing



Data points taken over 3 days at 38.6 ºC, from two separate pressurisation/depressurisation cycles, while ambient pressure varied between 1018 and 1031 mbar.

Excludes data points during initial pressurisation.

Figure 24: Volume and Pressure During Bench Test of Variable Rate Delivery

The graph above demonstrates the relationship between internal syringe pressure and volume rate. Relating pressure directly to rate does not work well at high or low rates and would be a poor method of directly controlling drug delivery because of this.

The next graph demonstrates the variable delivery rate ability.

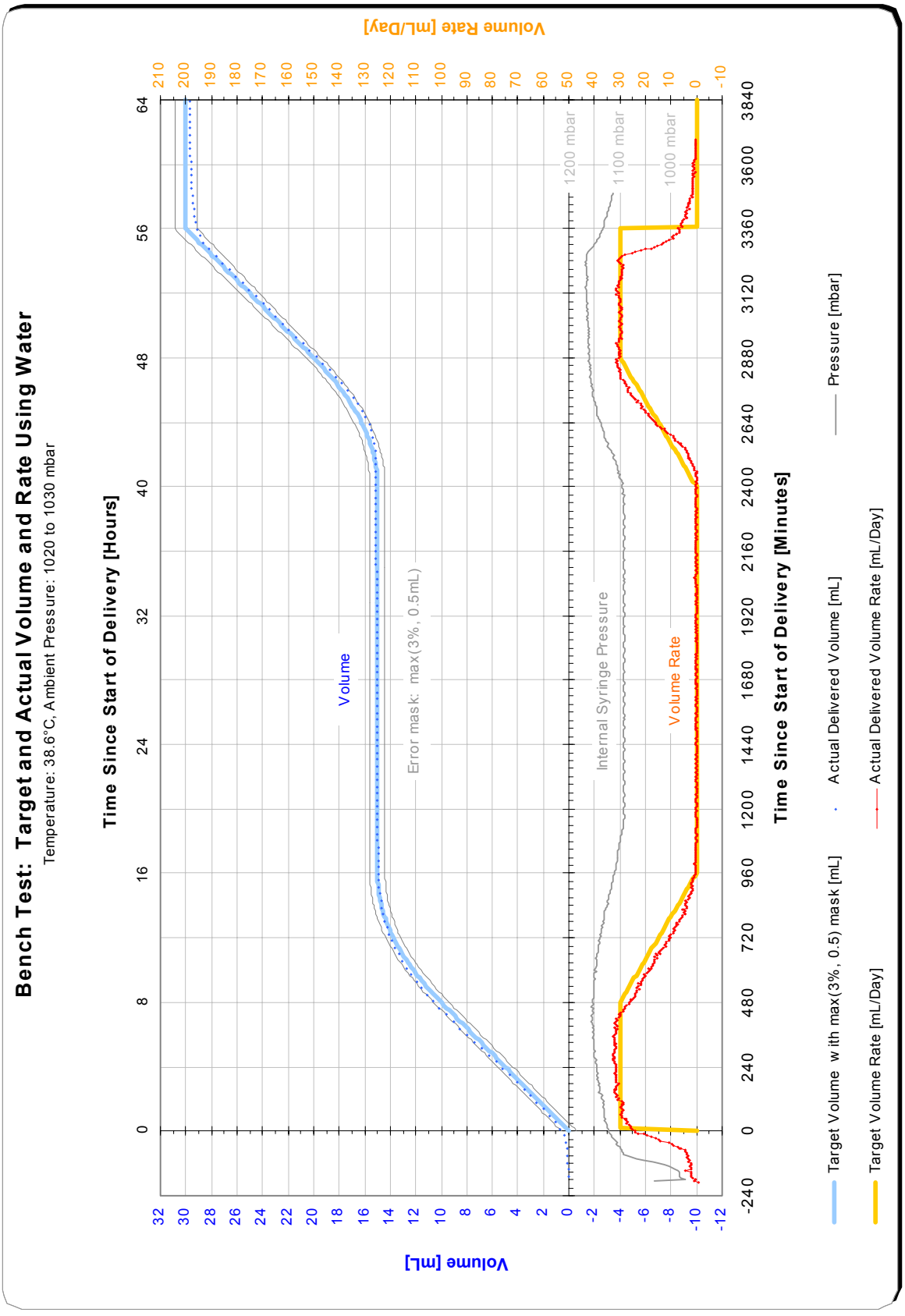

Bench Test: Target and Actual Volume and Rate Using Water
Temperature: 38.6°C, Ambient Pressure: 1020 to 1030 mbar
Time Since Start of Delivery [Hours]
Time Since Start of Delivery [Minutes]
Volume [mL]
Volume Rate [mL/Day]
Volume
Error mask: max(3%, 0.5mL)
Internal Syringe Pressure
Volume Rate
1200 mbar
1100 mbar
1000 mbar
Target Volume with max(3%, 0.5) mask [mL]
Actual Delivered Volume [mL]
Pressure [mbar]
Target Volume Rate [mL/Day]
Actual Delivered Volume Rate [mL/Day]

Figure 25: Volume and Volume Rate During Bench Test of Variable Rate Delivery

The actual volume delivered was obtained by placing the syringe on scales inside an oven maintained at 38.6°C. The syringe was set up to drip over the edge, meaning that a decrease in mass represented an increase in volume delivered.

The scales had a resolution of 0.01g and were set to output digital mass data directly into a spreadsheet every 15 minutes. The accuracy of this technique allowed an estimate of mass loss due solely to evaporation out of the syringe orifice. The syringe orifice is approximately $1mm^2$ in area producing an evaporative loss of around 30µL a day.

With temperature fixed at 38.6°C, ambient pressure varied ±5 mbar, which is the temperature and pressure variation expected inside the cow. Other factors not simulated on the bench were the constant movement, more sudden pressure changes and slight mechanical squeezing of the syringe body that would be expected in the cow. These were neglected to obtain an accurate understanding of the delivery mechanism in isolation.

The actual volume and actual volume rate traces have been advanced with respect to the targets by 100 minutes to take account of the average syringe delay. This could alternatively be done in software. The actual delay would still be present, but the user would not have to manually shift the response trace.

The ±3% accuracy is good, especially considering the fact that this test profile was designed to pick out the shortcomings of the syringe based system. At time equals zero, a step change in desired volume rate is not suited to the gradual nature of the gas producing pressure pump, but there is less that 0.5mL error during the start of delivery. Constant rate delivery till 480 minutes is very acceptable and the gradual decrease in target rate after that accommodates the fact that the syringe does not cope well with having to stop quickly.

The 24 hour period of zero delivery between 960 and 2400 minutes is designed to test the pressure leak compensation mechanism. The small bumps in the pressure trace during this time are due to the gascell maintaining constant pressure by switching on occasionally. At 2400 minutes, the syringe is asked to start delivering at an extremely low rate after a long period of inactivity.

This should cause it some problems as the static friction on the piston is higher than the moving friction. It sticks for a while, but catches up again by 2880 minutes. The remaining short fall is due to the fact that the leak compensation holding pressure while not delivering must be a certain amount below that required to make the piston move. This is to make sure that no volume is delivered during this period. Due to this, a small amount of gas supposed to start the piston moving, is actually used simply to increase the pressure again to that point. This results in a small delivered volume deficit from that point onwards.

At 3360 the rate undergoes another step change: this time to zero. The syringe internal pressure relaxes towards ambient slowly, but the total volume delivered is within the greater of 3%, or 0.5mL of the target value at all times.

After a successful bench test, it is natural to question whether this accuracy will transfer through to an in vivo application of the device. Fortunately, Bunt, Rathbone, et al. (2001) had previously determined that in vitro and in vivo rates of vehicle delivery using the Theratron© syringe are essentially the same. Their experiment used a fixed value load resistor over a 7-day period with a sample size of three. Figure 26 shows their results.

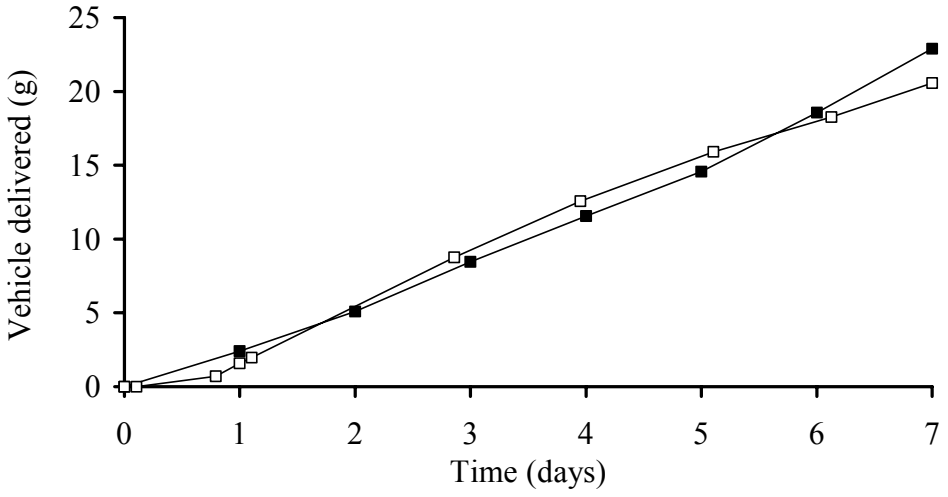


Figure 26: In vitro (□) and In vivo (■) Rate of Delivery
(Bunt et al. 2001, 28)

To save space here, all other data that the DMU is capable of generating is presented in the form of real data downloaded over the wireless link from the in

vivo experimental results in the next chapter.

3.14 Specifications

The major specifications and benchtop performance of the DMU system are presented in the following table.

Table 7: DMU Specifications

Overall	Operational temperature range	-10 to +50 °C dependant on properties of solution being delivered
	Operating voltage	3.0V nominal
	Battery life	4 to 7 weeks dependant on usage profile
	Sleep current	120μA. While integrating current at 36Hz and listening once a second for wireless data
	Peak current	17mA
	Dimensions	Electronics package: 28.6x28.6x25.0mm Body: 30x30x150mm including drug reservoir but excluding antenna and retention device
Controlled Release Delivery	Payload	40mL
	Maximum rate	60mL/day sustained, up to 120mL/day in short bursts
	Volume accuracy[4]	3% or 0.5mL, whichever is greater
Transceiver	Transmit output power	-6dBm (0.25mW)
	Range	40m outside (typical)
	Raw data rate	23kBPS
	Modulation	On-Off keying
	Carrier frequency	433.92MHz
	Carrier frequency tolerance	±200kHz
	Receiver dynamic range	-10 to -84 dBm

[4] Benchtop testing at constant temperature with pressure allowed to vary ±5 mbar

4. Experimentation

4.1 Materials

4.1.1 Vehicle Formulation

The delivered vehicle was aqueous HydroxyPropyl MethylCellulose (HPMC) solution. The HPMC was United States Pharmacopoeia substitution type 2910 (Shin-Etsu Chemical Co. Ltd.) at 4% weight per volume in double distilled water. The manufacturer's data sheet gave the viscosity of the solution as 4000 cP at a body temperature of 38.6°C. This formulation had previously been used as a vehicle for progesterone in the Theratron® syringe (Bunt, Rathbone, Ogle, and Morgan 2001, 28), but on this occasion was used without any pharmaceutically active agents. This blank vehicle simulated the administration of a typical drug in solution.

4.1.2 Drug Delivery and Monitoring Units

The intended function, operation and construction of the DMU's and base station have been extensively described in the previous chapter. Schematics, printed circuit board layout and bill of materials including individual component descriptions and their purpose are presented in appendices A through E. Electronic versions of these and the source code for the programs are provided on the accompanying CD-ROM inside the back cover.

4.1.3 CIDR®

Each DMU and the control syringe had an active CIDR® attached for retention

purposes. Using an active CIDR® meant that the cows would be prevented from reaching estrus during the experiment. This meant that behavioural and physiological changes due to estrus were not expected to occur (e.g. vaginal temperature peaks due to ovulation would not occur.)

4.1.4 LiveLube

LiveLube was used as a lubricant during DMU insertion.

4.1.5 Animals

The five cows were part of the Dexcel Ltd. research trial herd on the Number 4 station on Ruakura Road, Hamilton, New Zealand. All cows were of the Friesian breed, between two and five years old, weighing approximately 500kg each. Ovaries were intact and the cows had been cycling normally prior to the experiment.

4.2 Methods

To answer the thesis objectives, the delivery and monitoring performance of the DMU was demonstrated in a week-long field trial. Four cows each had a DMU loaded with 40mL of HPMC inserted into their vagina. A fifth cow had an HPMC filled syringe inserted without a DMU for control purposes. Figure 28 shows the DMU in vivo.

Periodic withdrawal of the devices allowed for a visual check of piston position to compare actual and intended delivered volume. Figure 27 shows a DMU temporarily removed for that purpose. Removals were kept to a bare minimum to reduce stress in the animals.

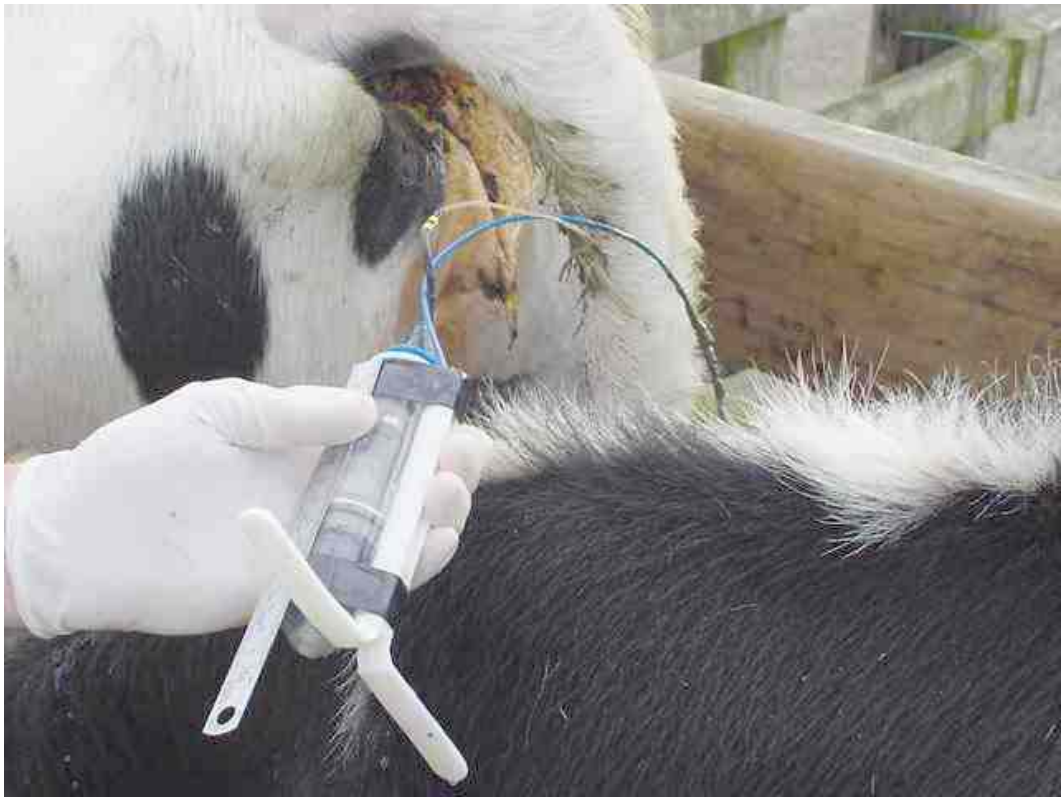


Figure 27: Removal For Inspection and Piston Position Check

Figure 28: DMU In Vivo

4.2.1 Animal Manipulation

Dexcel technicians carried out all animal manipulations. Each day, the cows were herded from the paddocks into bales to facilitate insertion, removal, data exchange and observation. The DMU's were inserted by the trained Dexcel technicians with the aid of LiveLube by hand as per Figure 29 on the first day. The cows were allowed to free roam in paddocks after their daily inspection.

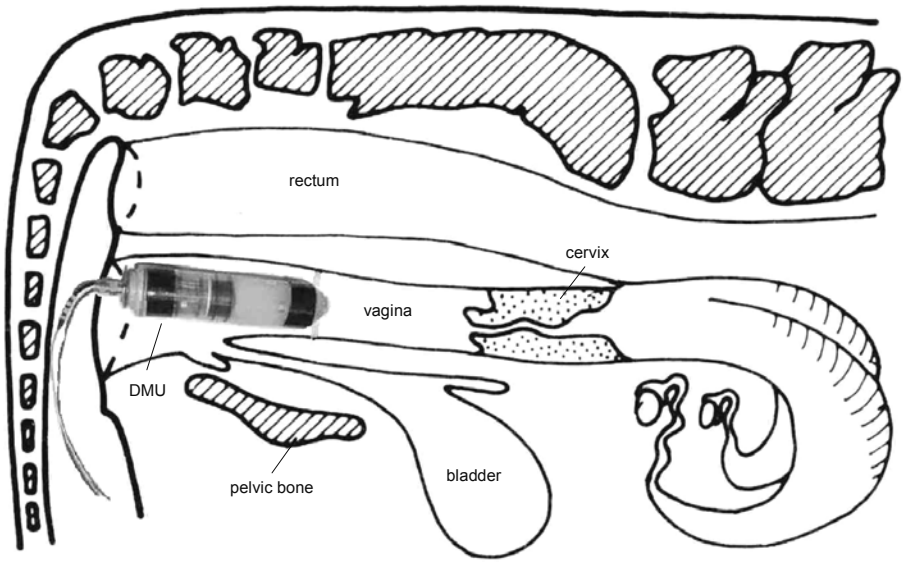


Figure 29: Location of DMU in Cow
Adapted from (Webster 1993, 2)

4.2.2 Ethics Approval

Ethics approval was obtained from both the Ruakura Research Centre Ethics Committee (approval number IDC 039 14) and the Ethics Committee on the Welfare of Experimental Animals at The University of Waikato in compliance with their Code of Ethical Conduct for the Use of Animals for Teaching and Research and section 83 of the Animal Welfare Act 1999.

4.2.3 Delivery Programme

Two different profiles were employed. Two of the devices were set to deliver at a

constant rate of 4.29 mL/day, delivering 30.0mL over 7 days. The remaining two had the same variable rate profile used in the bench test in the previous chapter, but scaled in rate and time to deliver over a week instead of three days. The maximum rate in the variable rate profile was 10mL/day, also resulting in 30.0mL total delivery at the end of that time. This variable rate profile can be seen in Figure 30.

To ensure the devices were operating correctly, they were pressurised and activated before insertion. Approximately 3 mL of the vehicle was delivered prior to insertion to confirm correct operation.

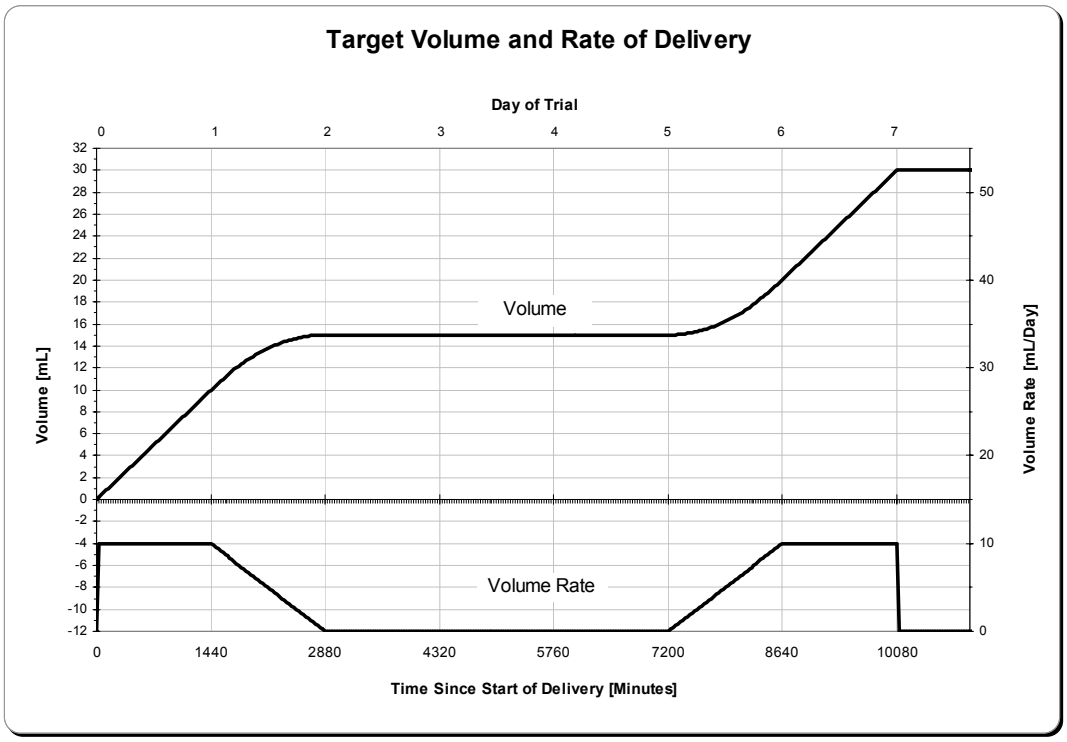


Figure 30: Variable Rate Profile Used In DMU's 1 and 2

4.2.4 Control, Monitoring and Results Collection

The program in the DMU took a reading from each of its environmental sensors every 15 minutes which was logged to memory. The power supply and drug delivery readings were also logged at this time. In theory, it was only necessary to download the results at the end of the 7 day trial because there is enough

memory for 720 sets of readings. In practice, downloading was carried out once a day in case the devices failed unexpectedly.

To demonstrate the external control ability, the delivery program for DMU 3 was manually overridden via the wireless link. The first external control period aimed to inhibit delivery for a 24 hour period. The second external control period aimed to inhibit delivery for a 48 hour period.

4.3 Results and Discussion

The following results consist mainly of graphs generated by downloading logged data from DMU 3 over the wireless link during the experiment. DMU 3 was the only DMU to last the whole week.

DMU 1 and 2 stopped communicating after 48 hours. DMU 4 stopped communicating after the first day. Further observations relating to these devices and the control syringe are presented in Appendix A: Additional Experimental Results.

Most of the data was downloaded during the daily observation period with the cows confined to bales. Data was also successfully downloaded from an adjacent paddock with the cows going about their normal activities.

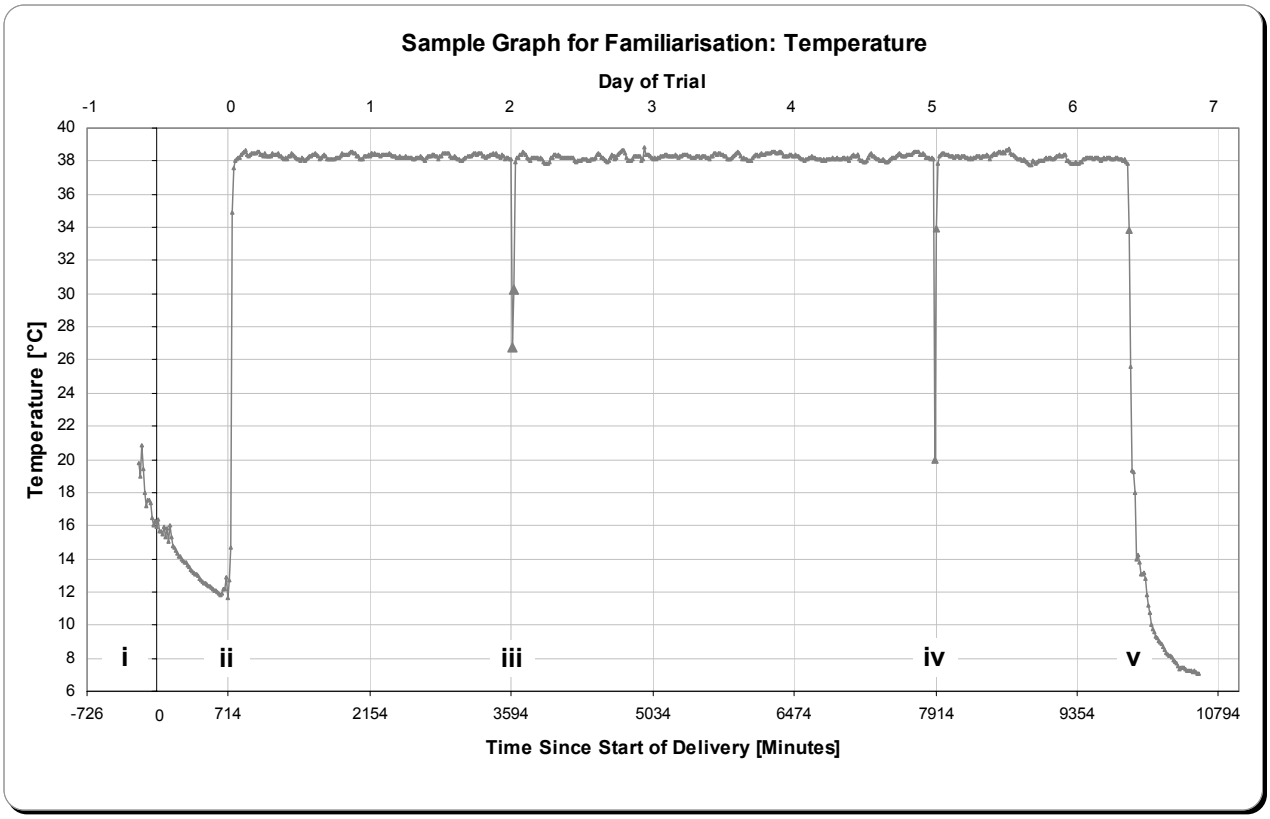
4.3.1 Trial Conditions

The first day of the 7 day trial was 23 May 2001. Throughout the experiment, ambient temperature ranged from a minimum of 1°C at night to a maximum of 16°C throughout the day. Pressure ranged between 1016 and 1028 mbar.

4.3.2 Explanation of Graph Data

The following graphs from the experiment are derived from data downloaded over the wireless link from DMU 3. DMU 3 had a constant 4.29mL/day delivery profile.

Figure 31 is provided purely for familiarisation with the generic graph layout which exhibits some commonality with all remaining graphs. The trace in Figure 31 shows temperature, purely for the purpose of providing a concrete example. The actual temperature results are presented later.



i	-191 minutes: The DMU is turned on and the syringe begins to pressurise on the bench. (The delivery program does not start until 0 Minutes)
ii	714 minutes: DMU insertion into animal.
iii	3604 minutes: DMU removed for inspection and replaced after 10 minutes.
iv	7904 minutes: DMU removed for inspection and replaced after 10 minutes.
v	9874 minutes: The DMU fell out of the cow.

Figure 31: Sample Graph for Familiarisation

Each trace is made up of 720 data points sampled 15 minutes apart and joined with straight line segments. This provides 7 days worth of data. The vertical grid lines are equally spaced at 0815 each day. They are approximately aligned with the observation times since observations occurred at 0815 ±45 minutes. Exact

times are given in Table 8 of Appendix A: Additional Experimental Results.

The roman numerals across the bottom of the time axis signify specific events during the experiment and are repeated on all subsequent graphs as readily identifiable reference points:

i At –191 minutes, the DMU is turned on and the syringe begins to pressurise on the bench. 191 minutes later, at time = 0, the drug delivery program commences, but the device has not yet been inserted into the cow. The DMU continues to deliver on the bench for another 12 hours. During this time, approximately 2 mL of vehicle was delivered from DMU 3.

ii At 714 minutes after start of the delivery program, DMU 3 is inserted into the animal. This meant insertion occurred at 714 + 191 = 915 minutes after power on reset, or 0900 on day zero.

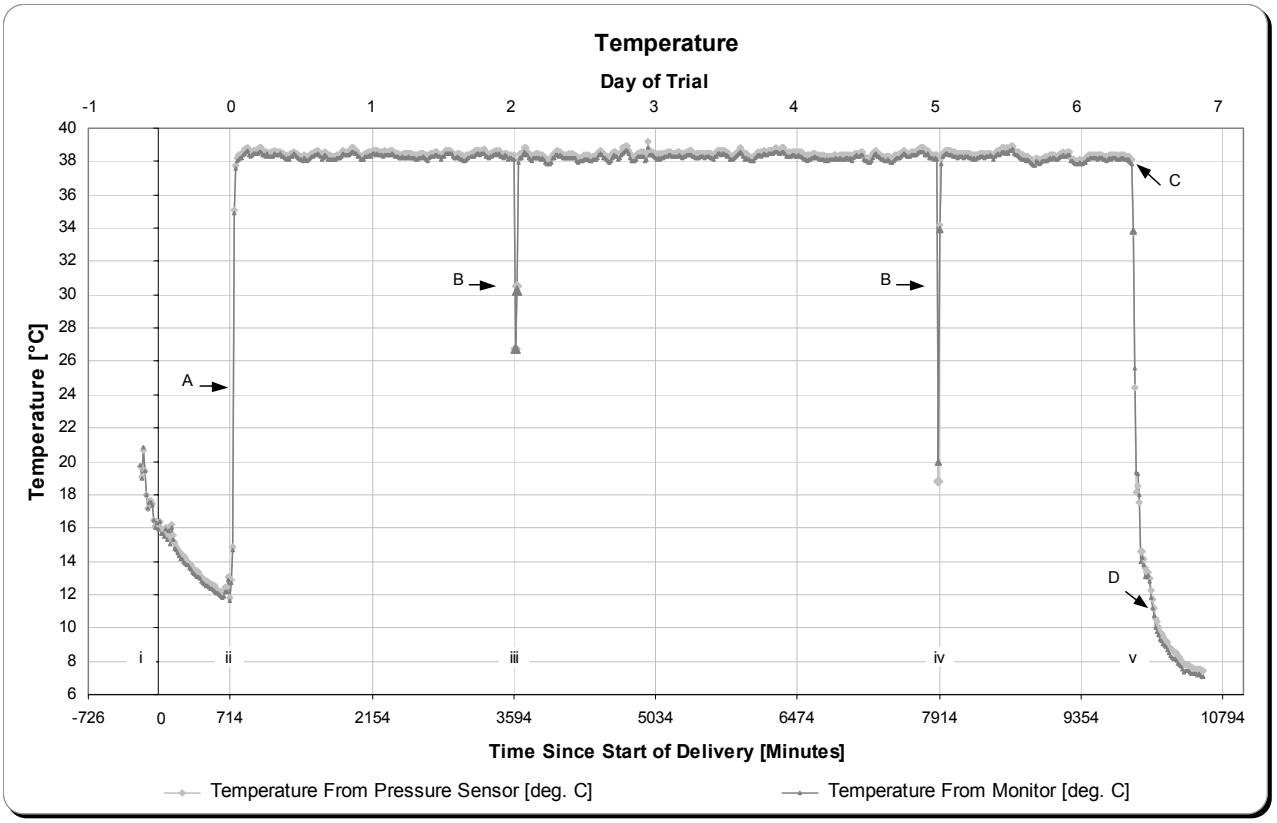
iii At 3604 minutes the DMU is removed for inspection and replaced after 10 minutes.

iv At 9874 minutes the DMU is removed for inspection and replaced after 10 minutes.

v The DMU fell out of the cow of its own accord.

4.3.3 Temperature

Results



A	When the DMU is inserted, both temperature sensors increase rapidly from ambient, reaching 38.4 °C. They both remain within ±0.5 °C of that value while inserted.
B	When the DMU is removed for a piston position check, both sensors rapidly cool and take 30 minutes or so to reheat once re-inserted.
C	This is where the DMU fell out of the cow of its own accord.
D	The temperature falls rapidly to ambient in exponential fashion.

Figure 32: Downloaded Results: Temperature

Discussion

Average temperature while inside the cow is 38.4°C, which is in agreement with the nominal 38.6°C reported in the literature (Webster 1993, 2).

Even when the temperature scale is magnified greatly, no diurnal oscillation is

evident in the time domain. However, Fourier analysis shows there is a significant 24 hour oscillation present.

To prepare the data for Fourier analysis, 512 temperature readings from days zero though five are processed as follows:

- Six points are artificially low due to the fact that the DMU had been removed on occasion to check the piston position. These points are replaced by the value of measured body temperature immediately preceding them.
- The points are smoothed with a median filter.
- The mean temperature is subtracted from each point to remove any DC level. This is necessary because the DC smudge would otherwise swamp the low frequency component of interest.

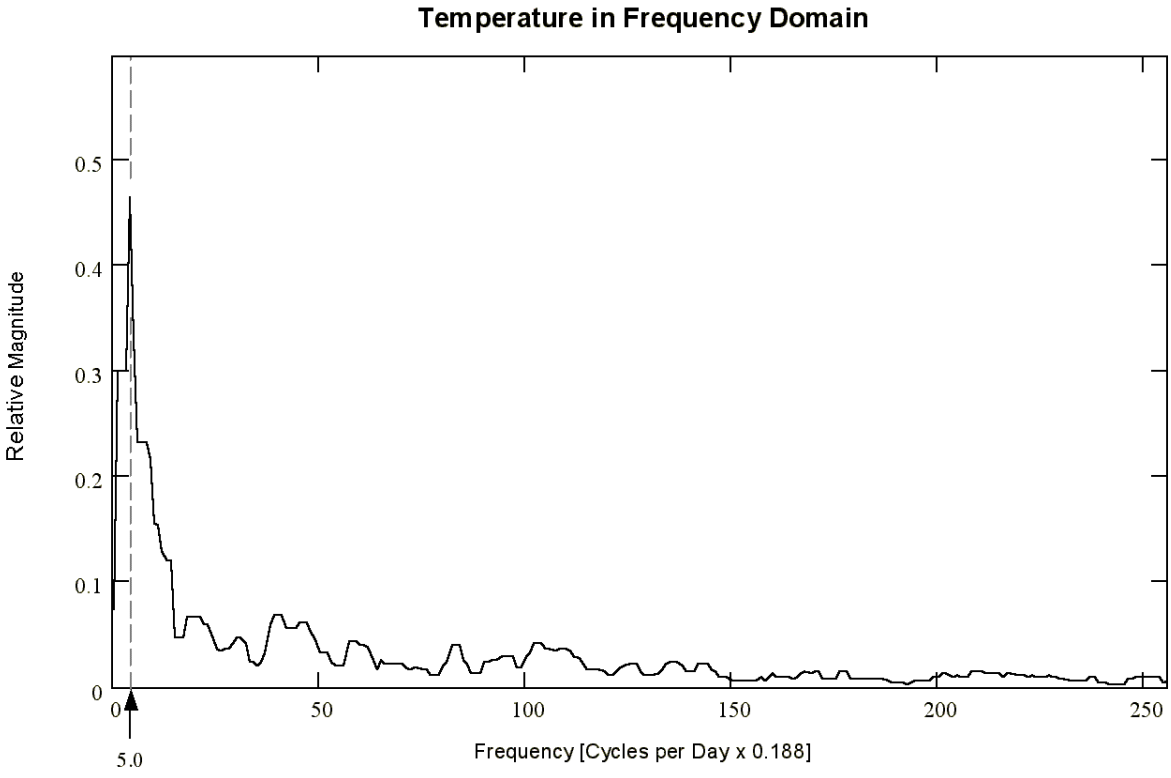


Figure 33: Downloaded Results: Temperature in Frequency Domain

The frequency resolution is reasonably coarse. The 255th discrete value on the right of Figure 33 represents half the sampling frequency, or 48 cycles a day. Therefore, the frequency resolution is 48 / 255 = 0.188 cycles per day. The peak value occurs at 5 on the raw FFT frequency axis. This corresponds to 5 x 0.188 cycles per day, or, a period of 1.06 days. This is the diurnal variation in ambient temperature and animal metabolism.

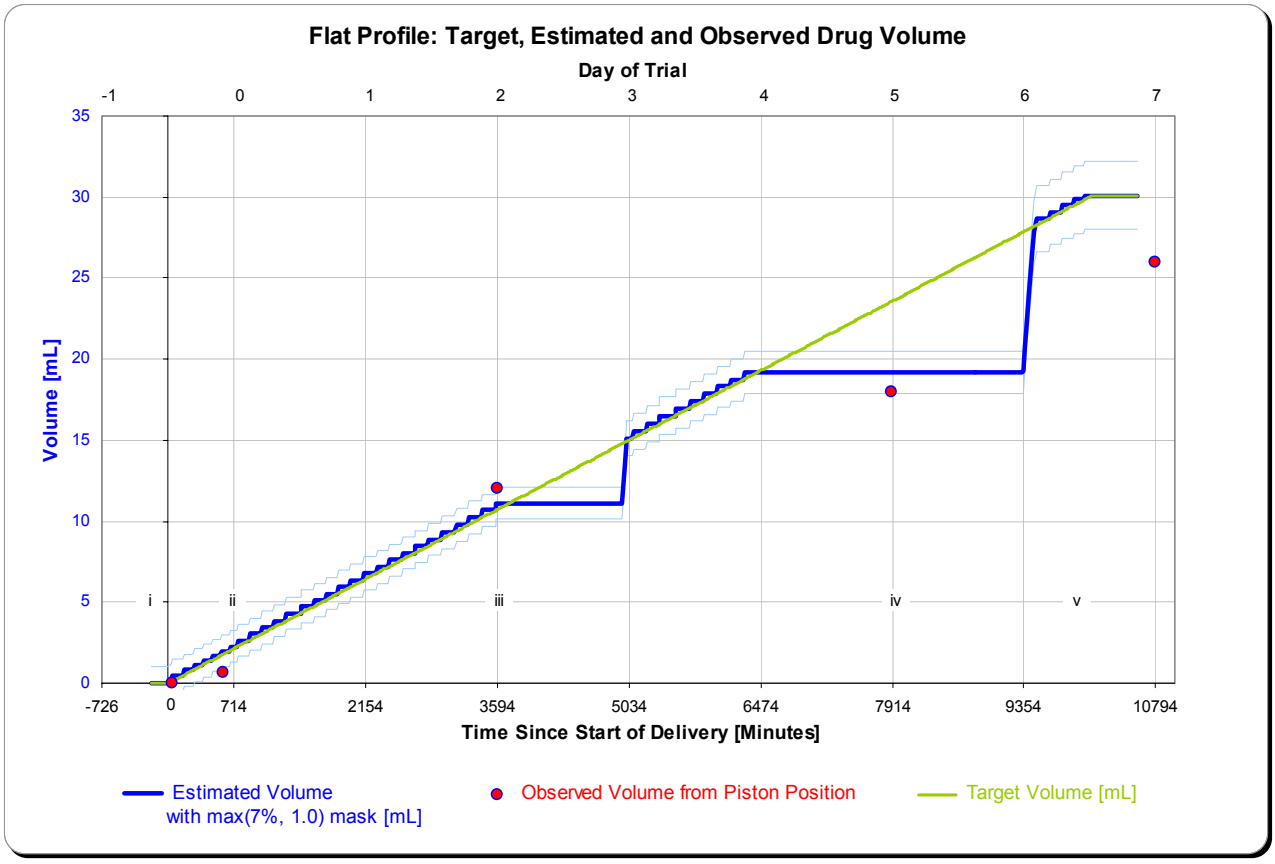
Fourier analysis of the measurements taken from the other temperature sensor resulted in a very similar frequency spectrum.

4.3.4 Volume Delivered

Results

The variable rate DMU's stopped working after day 3, however, there was enough data gathered from them to demonstrate variable rate delivery in vivo.

The graph below is from DMU 3 which was set to deliver at a constant rate of 4.29 mL/day. On two occasions during the delivery profile, external control was obtained over the wireless link. The internal program was overridden on day 2 by an external command to stop delivery for a 24 hour period. This process was repeated again for a 48 hour period starting on day 4.



Basic in vivo delivery accuracy is ±7% or 1.0 mL, whichever is greater. A mask of these dimensions is shown in light blue. The DMU fell out of the cow during the last few hours. This resulted in a piston position error in the last actual volume delivered point.

Figure 34: Flat Profile: Target, Estimated and Observed Drug Volume

The number of removals for piston position measurements were kept to a bare minimum to reduce stress in the animals. This means that there are only five check points on the actual volume delivered graph.

The points that were obtained prior to day 6 are within 7% of the desired delivery target. The light blue lines are a mask of 7% or 1.0mL, whichever is greater. The method for determining actual volume dispensed consisted of measuring the piston position from a datum using a steel rule as in Figure 27.

Discussion

As soon as external control was relinquished, the closed loop system made up the error as quickly as possible. This simplistic behaviour may be undesirable, but

demonstrates the basic closed loop control. An alternative behaviour would be to suspend target volume growth while the override is active. If it was important to keep the overall delivery programme on schedule, a sliding window delivery algorithm could be easily added instead. This would look at the difference in estimated and target volumes over a certain previous window period, rather than all the way back to the start of delivery.

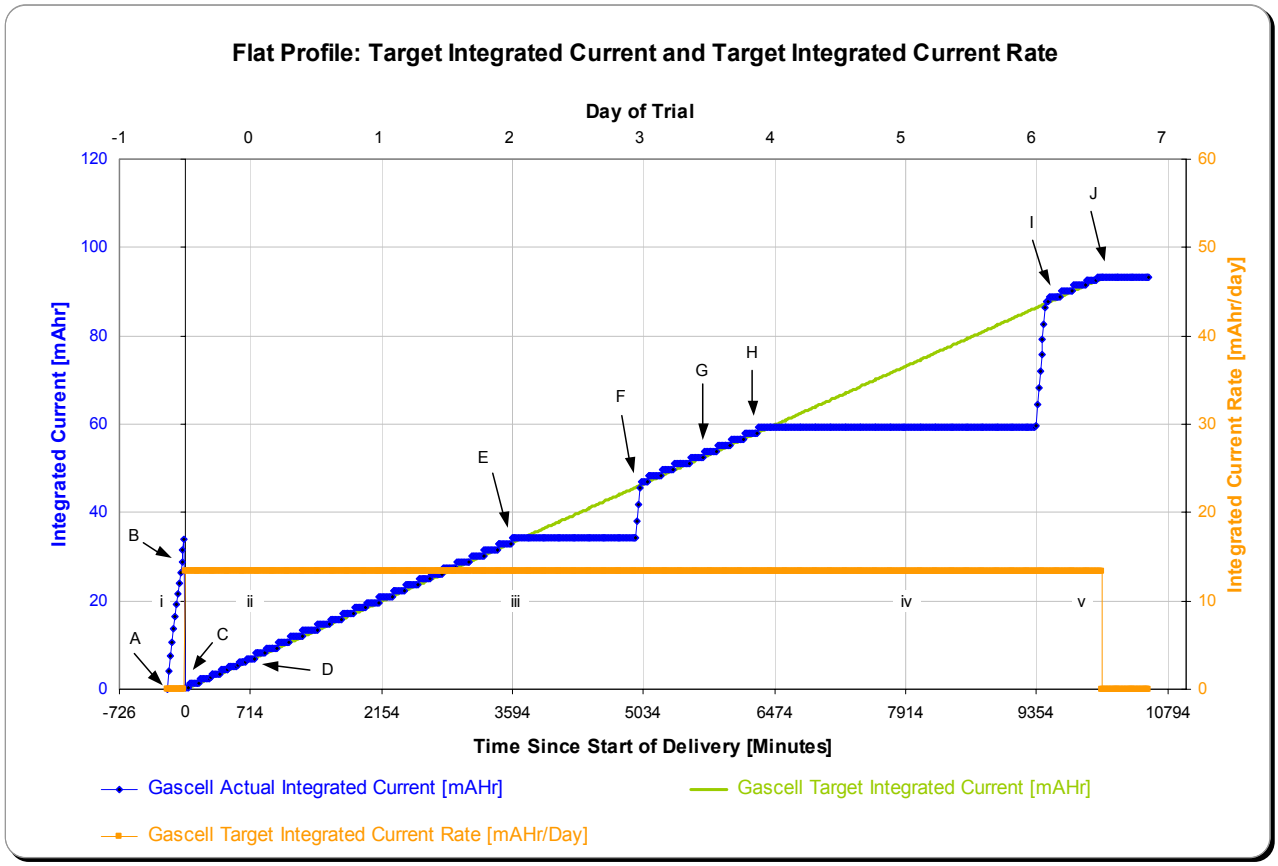
The last actual volume delivered point is the most in error because the DMU fell out of the animal shortly before this time. It would have been subject to greater error due to cooling and the rough treatment it experienced when it was dislodged from the cow and lay in the field for a few hours. When the DMU is not in the cow, cooling of the hydrogen gas makes it contract and the piston is sucked backwards a small distance.

There is some decrease in accuracy compared to the bench test. The loss in accuracy is attributable to the ever-changing environment that the DMU is subjected to inside the cow. This includes physical squeezing and other interactions produced by the cow as well as other more minor effects produced by the temperature and pressure of the day. Unfortunately, since only one DMU lasted to the first piston measurement, it is not possible to statistically assess the accuracy of delivery.

4.3.5 Integrated Current

Results

As you would expect, the integrated current graph is a scaled version of the estimated volume delivered graph, since they are related by a simple constant.

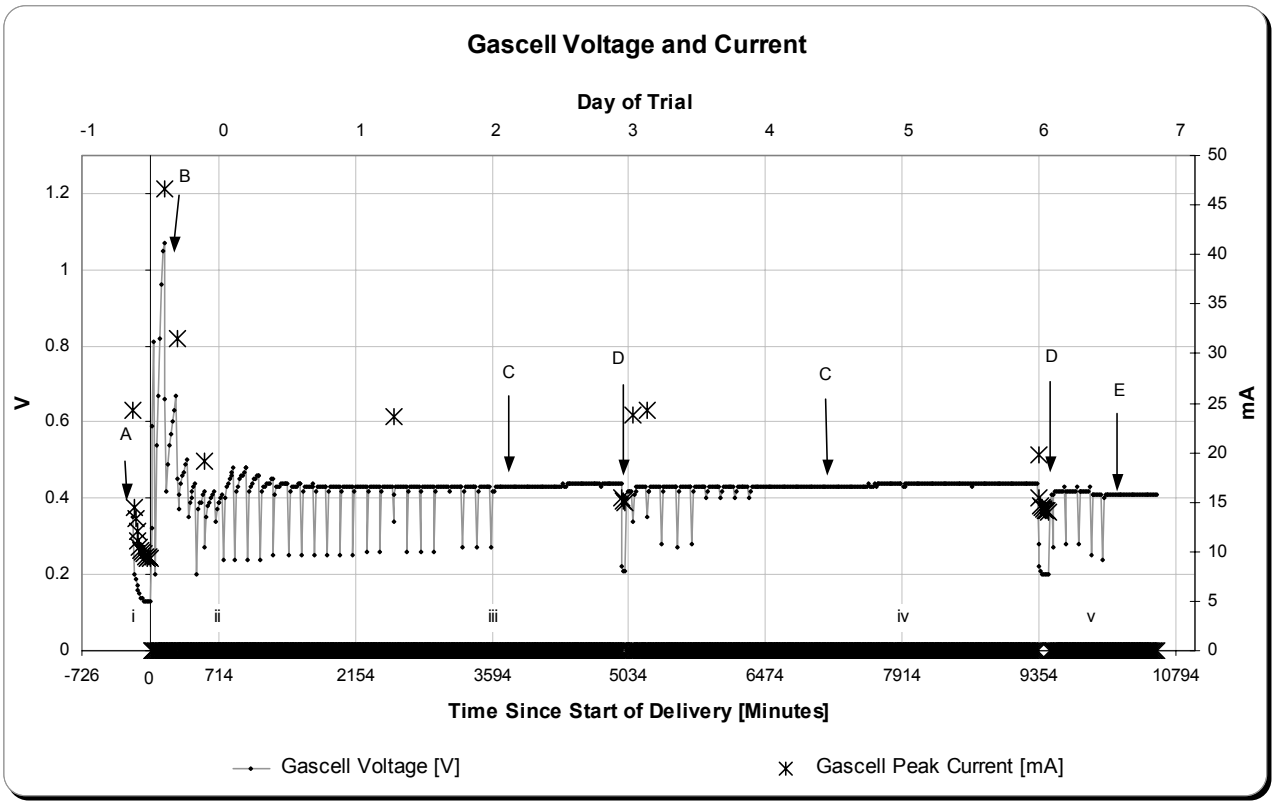


A	When the DMU is reset, it immediately starts to pressurise the syringe.
B	For diagnostic purposes, the integrated current accumulator is enabled so that a record of the integrated current required to obtain pressurisation is acquired.
C	When the syringe has pressurised, the integrated current accumulator is zeroed so that its value now represents the amount of volume delivered from that point onwards.
D	The integrated current accumulates in step like fashion since the gascell switch decision is made at discrete intervals of 5 minutes and integrated current accumulator is only logged every 15 minutes.
E	External control via a wireless command overrides the internal programme telling the gascell to stay off.
F	After external control is relinquished by another wireless command, the programme catches up to the target again as quickly as possible.
G	Progress continues as before.
H	Again, a wireless command overrides the internal programme.
I	Again, it catches up as quickly as possible when the release command is sent.
J	The target rate is zero from this point onwards, so there is no further increase in volume dispensed.

Figure 35: Flat Profile: Target Integrated Current and Target Integrated Current Rate

4.3.6 Gascell Voltage and Current

Results



A	At first, the gascell is on a 100% duty cycle to make the syringe pressurise as quickly as possible.
B	The delivery programme has commenced. Every 5 minutes, the following decision is made: If gas production is below target, the gascell is switched on, else it is switched off.
C	During the external control periods, the gascell is never on.
D	Shortly after external control is released, there is a short period of 100% duty cycle while the delivery programme rapidly makes up for lost time.
E	The gascell is off from this point onwards because the delivery programme has finished.

Figure 36: Downloaded Results: Gascell Voltage and Current

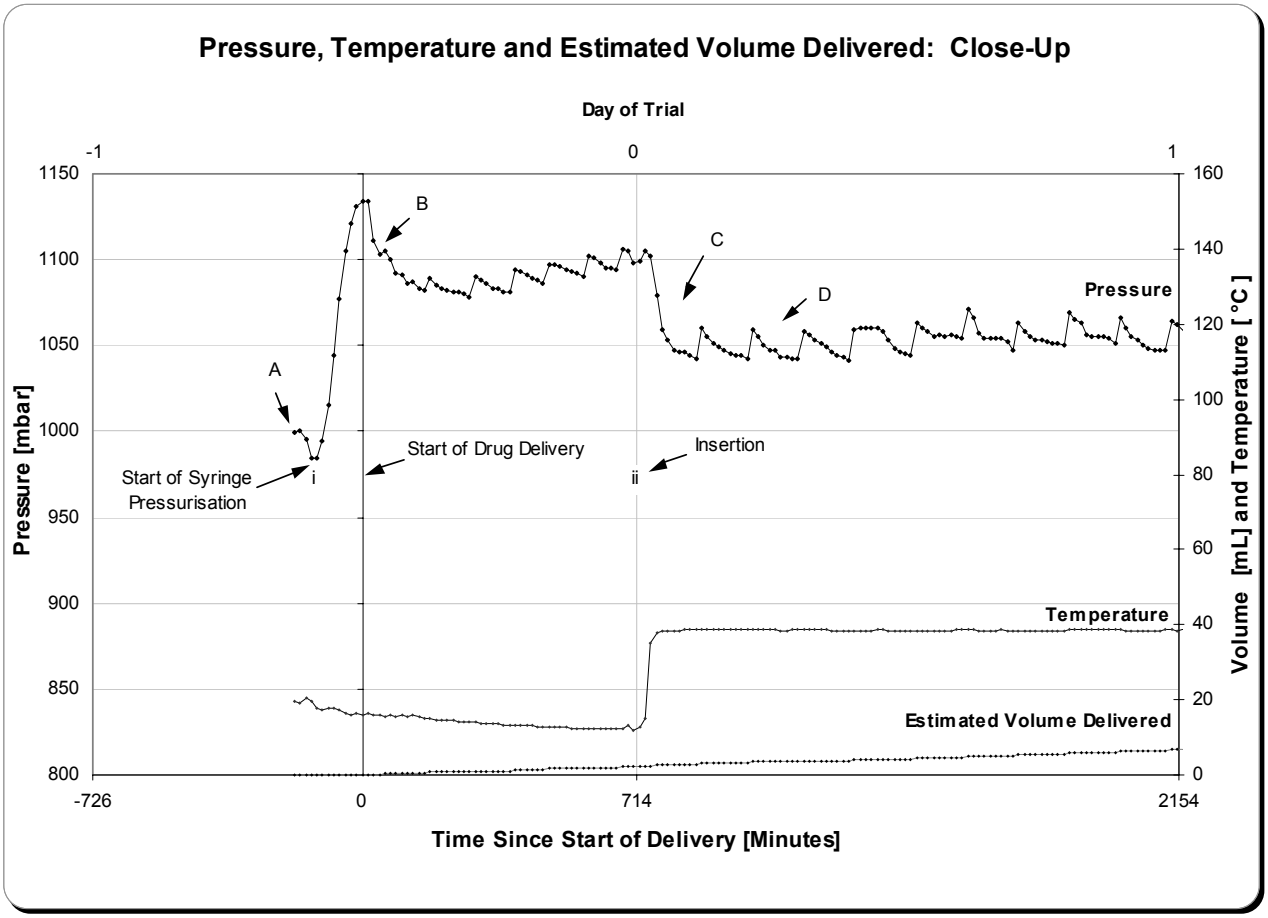
Discussion

The gascell switch decision is made every 5 minutes, but the data is logged only every 15 minutes. This explains why there are fewer non-zero current values displayed than you might expect.

4.3.7 Pressure

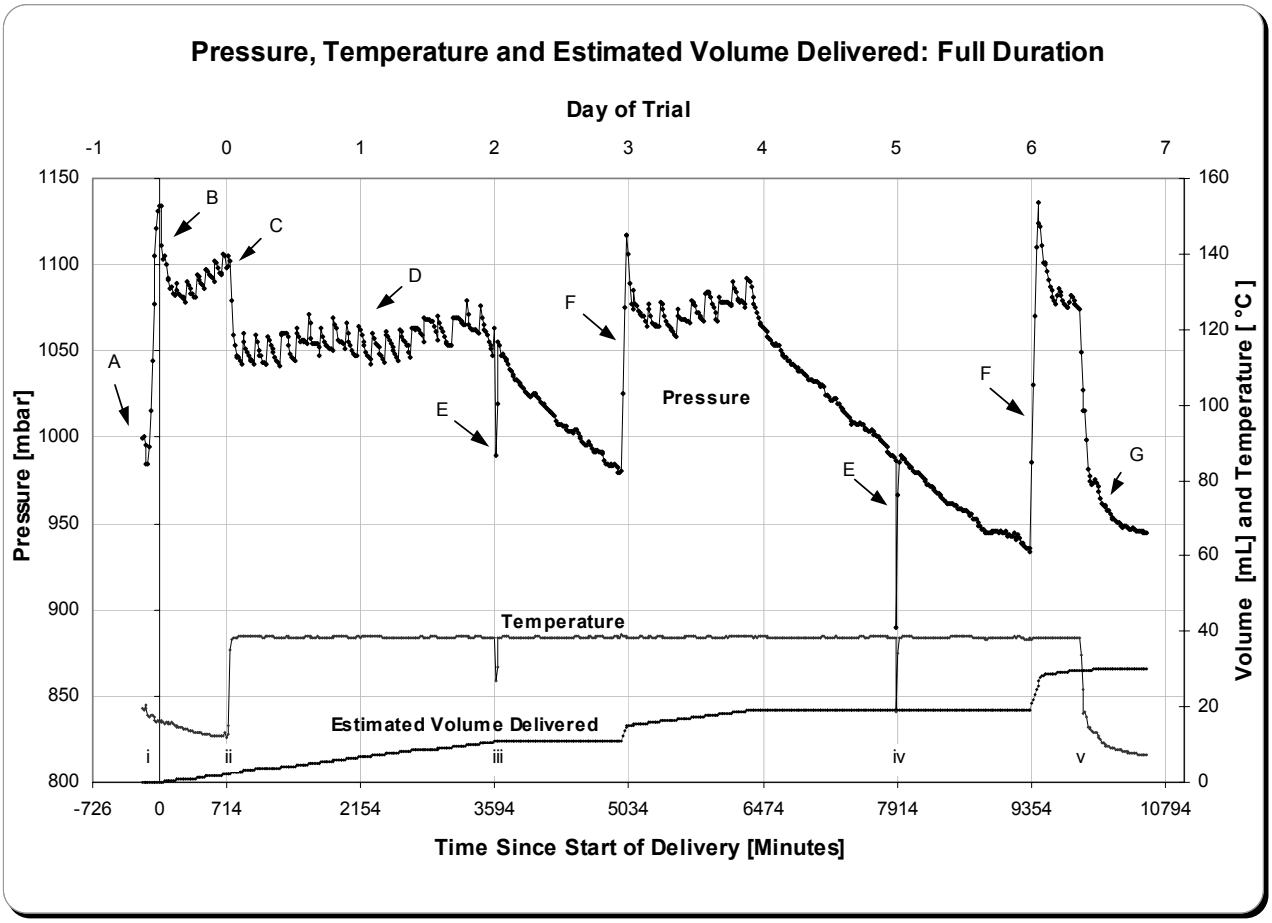
Results

Recall that the pressure readings are for internal syringe pressure which is an approximation of piston differential pressure. It is assumed that ambient pressure does not change significantly. The first graph (Figure 37) is a close up to allow examination of the pressure fluctuations during initial pressurisation and delivery.



A	When the electronics package is installed, the act of sealing the syringe increases the pressure to about 50 mbar above ambient. The gascell is switched on with a 100% duty cycle to pressurise the syringe as quickly as possible. Initially, consumption of oxygen by the gascell reduces the pressure to below ambient. Hydrogen production commences once all oxygen is consumed and the pressure increases until the piston starts to move.
B	All syringes were controlled with the pressure start override command via the wireless link so that they were synchronised with each other. At this point, drug delivery profile time has commenced (time equals zero on all graphs).
C	On insertion into the cow, temperature of the vehicle increases. There is a corresponding drop in vehicle viscosity. The resulting decrease in backpressure from the piston gives rise to a lower average pressure for the remaining part of this graph
D	Pressure spikes from individual active gascell periods are clearly evident.

Figure 37: Downloaded Results: Pressure, Temperature and Estimated Volume Delivered: Close-Up



E	Continuing from the previous diagram at point E, this point shows a sharp decrease and recovery when the DMU was removed for observation. When removed, the hydrogen cools and contracts very quickly resulting in this pressure decrease.
F	During the long period where the gascell was held off by external control, the pressure drops down toward ambient. When the catch up phase starts, pressure increases rapidly back to the delivery pressure.
G	Again, the hydrogen is cooler when out of the cow, resulting in contraction of the gas. The delivery programme also finishes at this point, meaning no further hydrogen is produced.

Figure 38: Downloaded Results: Pressure, Temperature and Estimated Volume Delivered: Full Duration

4.3.8 Cow Proximity

Results

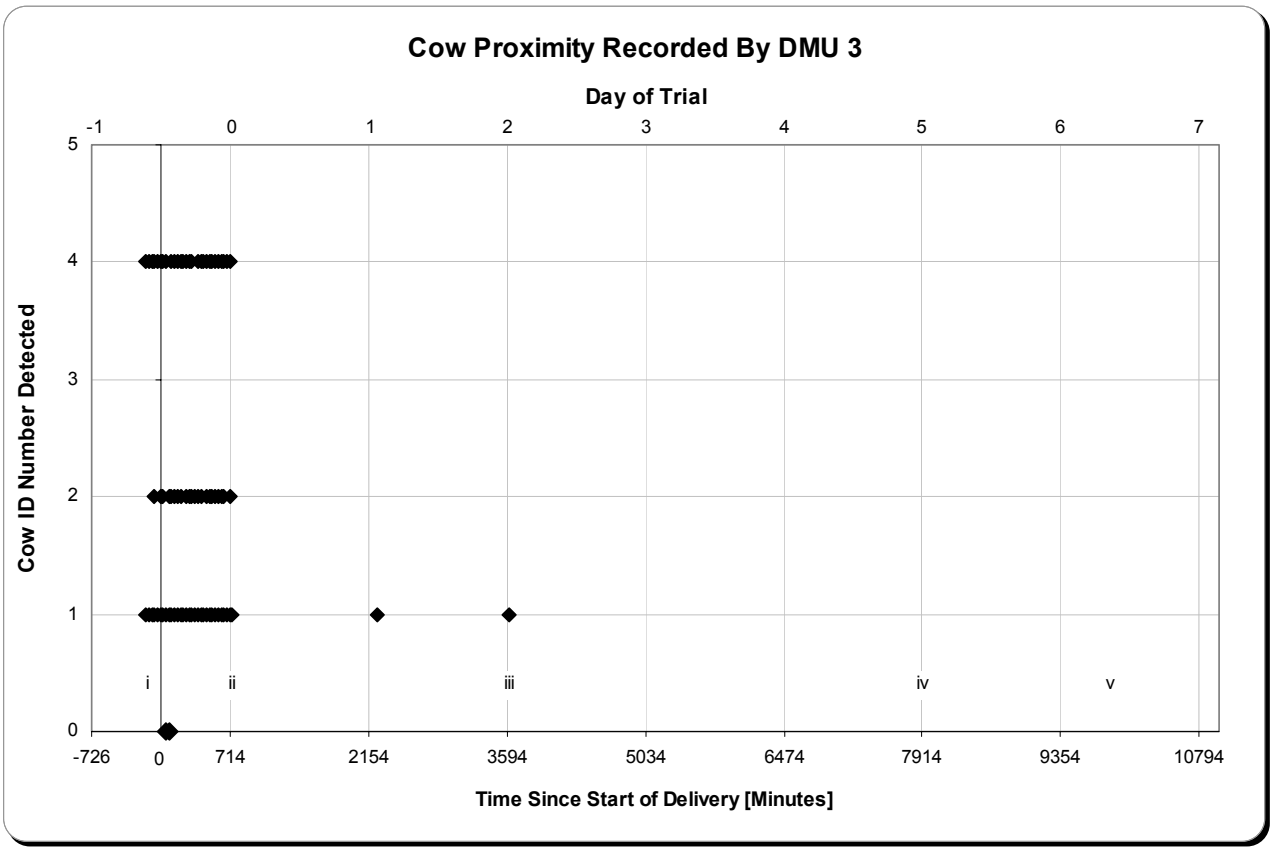


Figure 39: Downloaded Results: Cow Proximity Recorded By DMU 3

In these cow proximity graphs, the base station is represented with an ID number of zero. The reception just after time equals zero is a manual test initiated by the base station. A DMU cannot receive a transmission from itself when it is busy transmitting. This is why there are no transmissions recorded from DMU 3.

The following graphs show cow proximity data downloaded from DMU's 1 and 2.

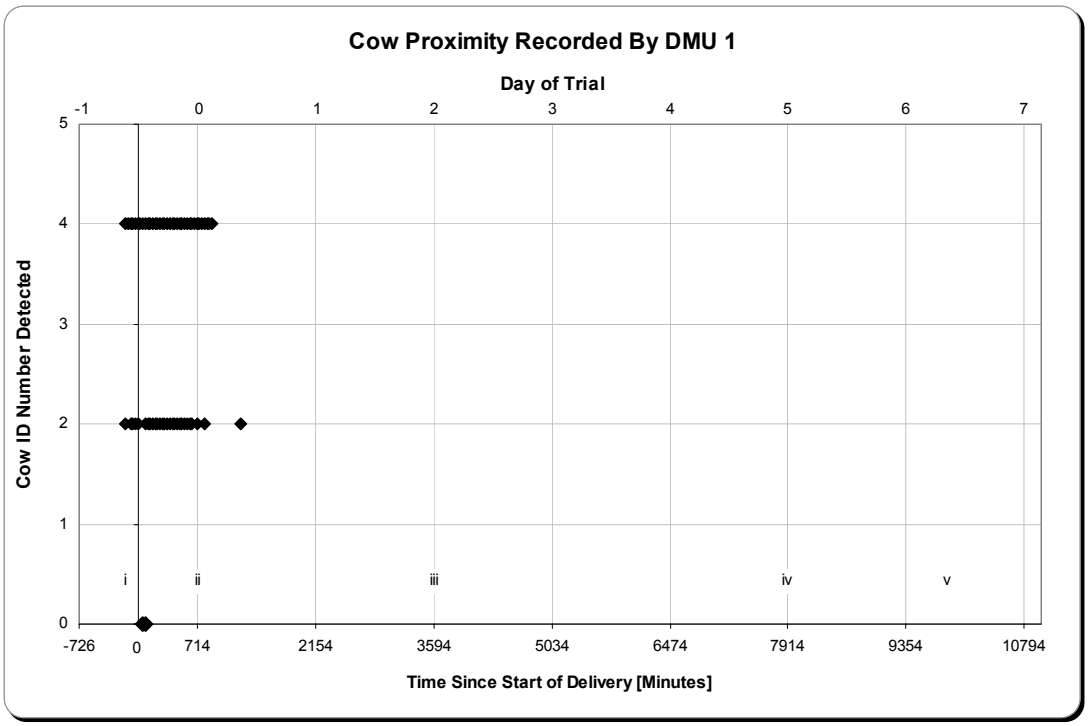


Figure 40: Downloaded Results: Cow Proximity Recorded By DMU 1

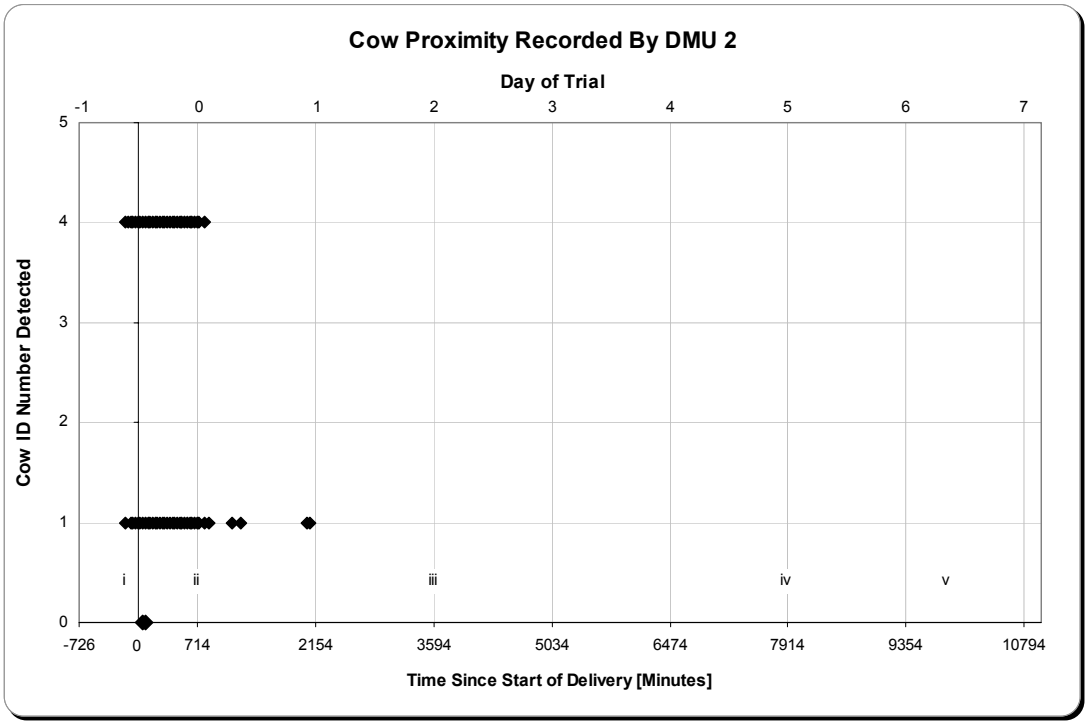


Figure 41: Downloaded Results: Cow Proximity Recorded By DMU 2

Discussion

Many successful transmissions prior to insertion were recorded. After that time,

only two inter-cow transmissions were seen by DMU 3. With the transceiver on DMU 2 only having a limited range, DMU 4 not responding after insertion and DMU 2 unable to respond after day 2, only inter-cow transmissions from DMU 1 were recorded by DMU 3.

4.3.9 Motion

Results

The vertical dashed grid lines are equally spaced at 0815 each day. They are approximately aligned with the observation times since observations occurred at 0815 ±45 minutes. Exact observation times are shown as triangles along the bottom of the graph and are given in Table 8 of Appendix A.

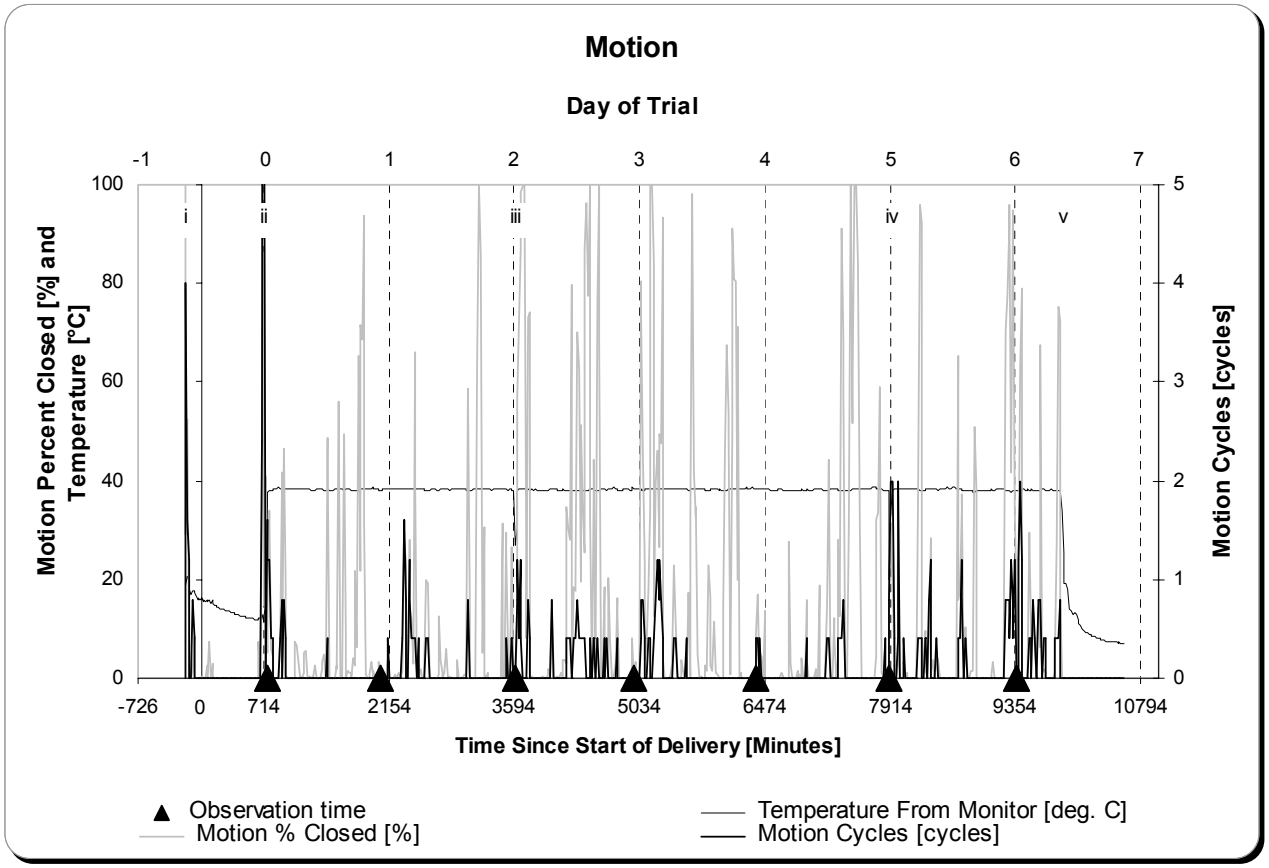


Figure 42: Downloaded Results: Motion

Discussion

Some peaks in motion cycle activity always correspond with the times that the cows were herded towards the yard for observations (triangles). There is a marked lack of activity in the hours just before dawn.

The fact that motion cycle peaks coincide predominately with the time of herding the animals toward the pens for daily inspection provides confidence that the motion cycle data is a good indication of general activity level.

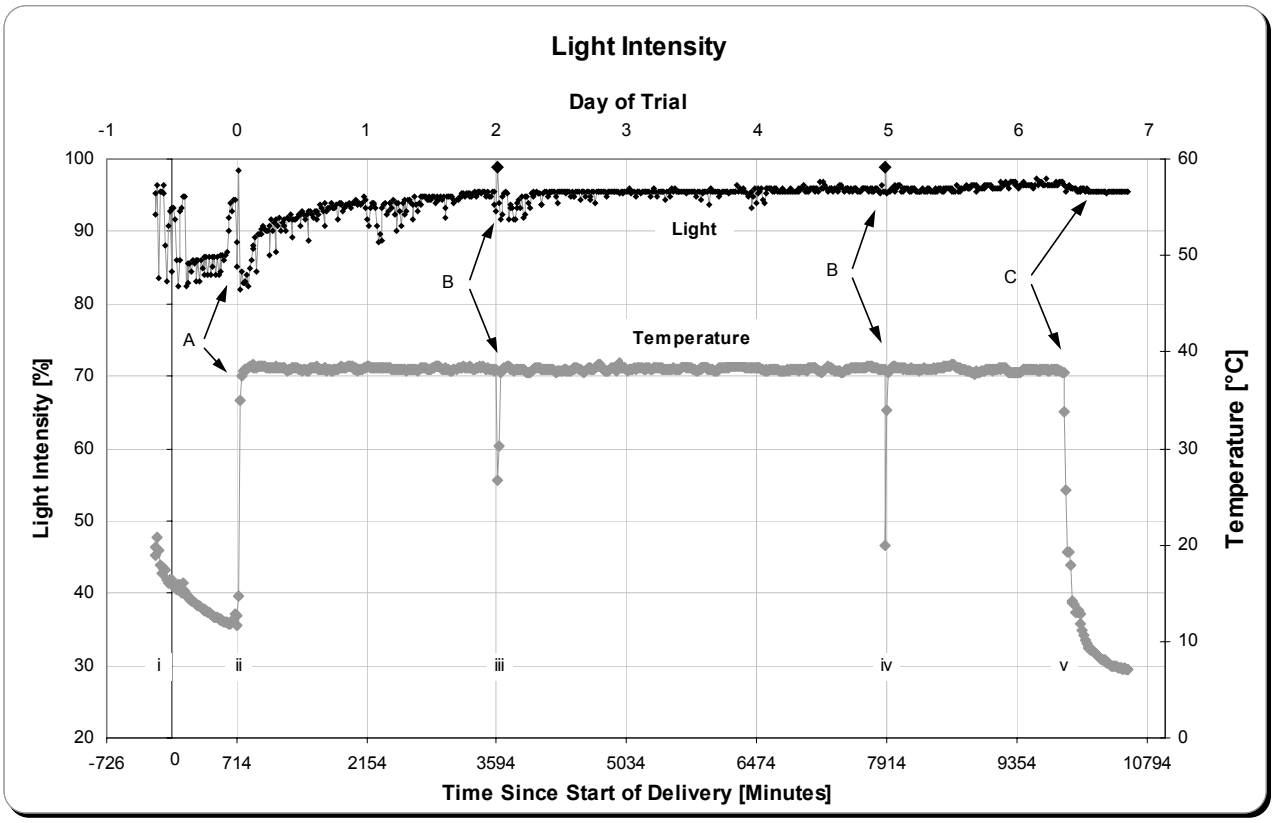
In contrast, the motion percent closed data needs to be compared with a comprehensive study of cow stance and behaviour over a number of hours before it can be considered useful. No in-depth observations were attempted in this first experiment so it remains unknown how helpful the motion percent closed data is.

All motion stopped when the DMU fell out. This proves that the motion sensor can assist in device self diagnostics.

Motion cycles has an arbitrary scaling for data compression which will be increased to provide better resolution in future, now that an idea of what the upper limit of the motion cycles inside a cow is.

4.3.10 Light Intensity

Results



A	The light reading takes a while to settle down after insertion.
B	When removed for inspection during daylight hours, the light reading shows a marked increase as expected.
C	After the DMU fell out, the light readings varied less and were below that obtained during the previous few hours. The value is below that obtained when removed for inspection because it fell out during the night.

Figure 43: Downloaded Results: Light Intensity

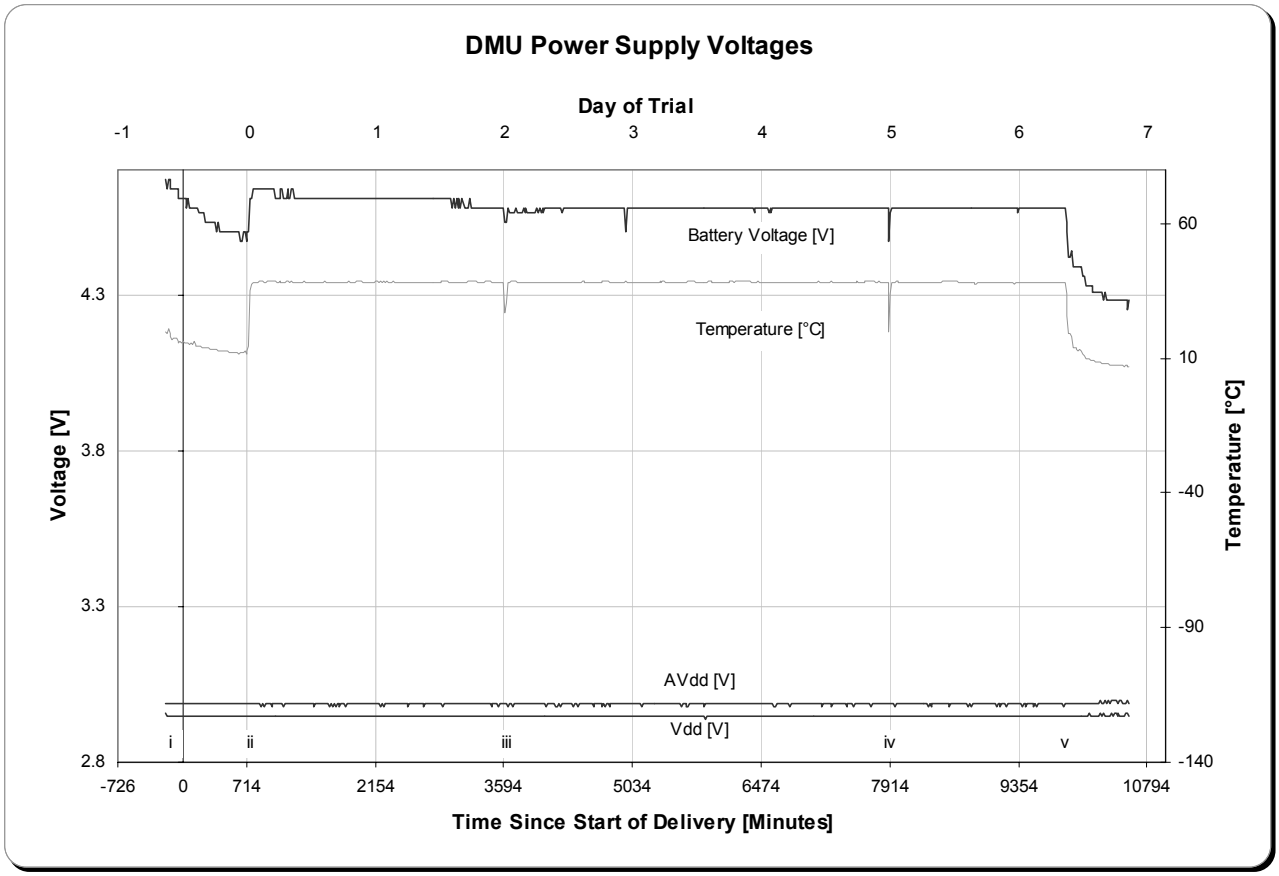
Discussion

Unfortunately, a programming error meant that the LED was kept on while light readings were taken. This explains why the light readings are unexpectedly high when inside the animal. Even so, the light intensity readings are of some value and indicate that a simple light sensor can be used to assist in a self-diagnosis role for the drug delivery hardware.

Light varied greatly in vivo. It is suggested that this is caused by the LED light being subject to total internal reflection from the syringe wall as the device moves around inside the animal. If confirmed, this might lead to a simple method of detecting what kind of material is in contact with the syringe near the LED, be it gas, flesh, or a thick layer of clear or opaque mucus.

4.3.11 Power Supply Voltages

Results



Battery voltage closely follows the temperature trace with an overall decline as time progresses. Even the sharp decrease in temperature on removal for inspection on days 3 and 5 has been captured by the battery voltage level.

Both the Vdd and AVdd regulated voltages remain constant as expected.

Figure 44: DMU Power Supply Voltages

Discussion

Starting at a no-load battery voltage of 4.65V on installation, on-load battery voltage stabilised at 4.50V after ten hours of operation. (On-load current is approximately 16mA.) At the end of the seven-day experiment this had fallen to 4.28V on-load. These voltages are quoted at room temperature. Voltage in the cow is generally 200mV higher due the increased temperature.

To assess its useful lifetime, the device was kept operational for a total of 40 days at room temperature without replacing the batteries. After this time, the on-load battery voltage was 3.92V. The minimum battery voltage for full-function operation is 2.70V (0.90V per cell).

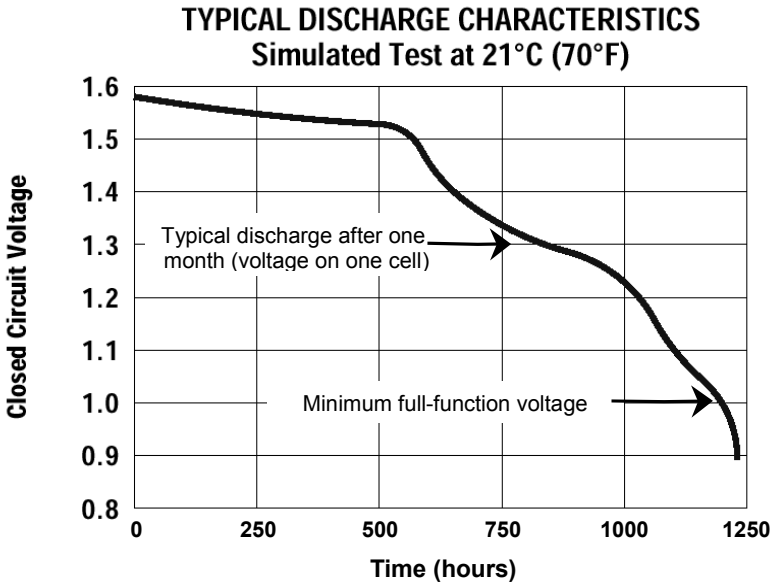


Figure 45: Discharge Curve of Energizer EPX76 Silver Oxide Battery
Adapted from EPX76 data sheet (Eveready Battery Company 2001)

During the experiment (first week), about five minutes per day of downloading was carried out on the device to ensure that the maximum amount of data was obtained in case it stopped working at any time. This uses up a lot of battery capacity. For the remaining weeks, a much more realistic download pattern was used. This explains why the voltage fell so much in the first week.

One month is probably the maximum period of reliable operational time with the

presently defined load profile and a reasonable download usage of one minute per day. If the user only downloaded once a week, seven weeks of operation could be expected in most circumstances.

The reason that a more precise answer cannot be given is that it greatly depends on the usage pattern of the device and the fact that battery voltage is often not a good indicator of the amount of remaining battery capacity. Battery voltage is influenced by the following factors:

- The voltage curve of silver oxide batteries is very non-linear as demonstrated in Figure 45.
- Battery voltage drops on a heavy load, then recovers slowly, so the recent load history affects the instantaneous voltage reading.
- Voltage is affected by temperature to a large extent as demonstrated in Figure 44.

If the sampling and download usage was very much less frequent, it is predicted that the batteries would last over a year. In practice, three weeks is more than adequate since insertion time is restricted due to animal welfare considerations.

4.4 Experimental Results Summary

DMU performance has been adequately demonstrated. Although three of the four DMU's had stopped working by the last day, enough data was gathered to prove the capability of the system. All systems worked very well except for the light intensity function. This had a restricted dynamic range due to the programming error already mentioned. It was still adequate to perform its primary function which is to help in assessing whether the DMU is correctly lodged in the cow.

In vivo delivery accuracy degraded to ±7% from the bench top performance figure of ±3%. This is a provisional accuracy figure since it was obtained from a single delivery run from the only DMU to last the full seven days.

5. Discussion

5.1 Performance Assessment

As a first field trial, the experiment was very much a success. Three of the four devices stopped working by day seven, but not before achieving all objectives. In particular, the following objectives were met:

- External control of drug delivery via radio link while in vivo.
- Precision controlled variable rate drug delivery in real world conditions to the specifications given in Table 7 on page 117. This means a basic accuracy of delivery of 3% on the bench, or 7% in vivo.
- Inter-cow communication for social grouping.

The wireless control and data exchange was carried out while the cows were marshalled into bales in the yard. Data download was also demonstrated successfully over a fence while the cows were in an adjacent paddock able to free range. This ability greatly enhances the usability of the system.

All of the initial requirements listed for the proposed delivery system on page 48 were satisfied. Delivery accuracy, transceiver range and battery life were better than required. These factors were important but hard to predict during initial design, so they had been given a generous safety factor early on.

An hypothesis was that animal ID could be easily incorporated into a drug delivery device if basic electronics were already present. Animal ID was added to the DMU with little effort.

5.2 Defect Analysis and Suggested Remedies

5.2.1 Antenna Positioning and DMU Retention

The environment is a potentially harsh one for the electronics. It was certainly not in the original design plan that cows would want to chew on the antenna! Fortunately, chewing of the antenna was not harmful for either cow or DMU. After one bite, the novelty seemed to wear off.

More of a concern was the fact that the antenna occasionally slipped inside the vulva meaning that communication with the devices failed at that point. This happened about 50% of the time and required a Dexcel technician to flick the antenna out before the data could be downloaded. This problem would be easily rectified with a stiffer antenna, possibly by attaching the antenna to the stiff plastic CIDR® removal cord. Alternatively, the antenna could be tethered to the animal through the use of a Kamar® patch, described below.

The DMU which fell out was found to have been inadequately taped. Separation of the syringe body and retention mechanism followed. This problem is easily solved by correct taping. A third band of tape in the middle is recommended in future for added security.

To help prevent against accidental loss of a DMU, the antenna could be tethered to the tail head of the animal. The Kamar® heat detection patches were mentioned in the section on estrus detection (page 22) and use a proven bio-compatible glue to fix a capsule to the coccygeal vertebrae of the tail head. Using this glue, it would be possible to tether the free end of the DMU antenna. The glue is strong enough to hold the weight of the DMU but would pull free in the event that the animal got caught in a fence.

Tethering by Kamar® patch would keep the device from straying too far into the vagina, keep the antenna in a position where it could receive and transmit properly

and, in the worst case, retain the DMU should it escape the vagina.[5]

5.2.2 Moisture Resistance

Being such a low power circuit, there are many high impedance pins that are susceptible to moisture. This problem was identified on the bench and an attempt at thwarting it by the use of an acrylic conformal coating was only partially successful. This could have been the reason why some of the DMU's stopped working after insertion.

The next step would be to use a silicone conformal coating, possibly with a Paralyne-C moisture barrier. Parylene C is a polymer which is used in aerospace and medical applications. It is deposited in vapour form under vacuum. The gaseous dimer molecules are split into monomers at temperature. When allowed to contact the item at room temperature, the gaseous monomers then polymerise to form a very tough, clear, impermeable membrane, only microns thick.

5.2.3 Battery Mounting

The battery clip solder joints were prone to cracking where they met the PCB. When cracked, this had the effect of reducing the clip pressure onto the battery. This sometimes resulted in unreliable battery contact and intermittent failure of the DMU.

The short term remedy is to re-solder the battery clips after about five or so battery changes. The longer term solution is to change the battery mounting and/or battery type.

One possible replacement battery is the CR2032 which is a 3V lithium manganese dioxide battery. The "CR" indicates that it can cope with high-load pulse currents. The Panasonic brand CR2032 has a 235mAhr capacity. The nominal voltage is 3V so two would be required in series.

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[5] The new taping procedure and use of the Kamar® patch has proved successful in subsequent experiments with Sensortec.

5.3 Critique of Design Process

It was stated previously that contemporary controlled release systems should be designed in advance of a particular use to provide a wider range of function and applicability (Rathbone 2000). Attention was paid to this design philosophy, but some compromise was necessary due to time and resource constraints.

The DMU is not independent of delivery route but can be adapted to different drug types, period of delivery and animal (within limitations). Many drug types that can be used in a vehicle of viscous fluid could be used. Period of delivery can range from a few hours to several weeks. The animal must necessarily be quite large due to the size of the DMU. Perhaps it could be used in horses without modification, although the retention mechanism might need modification.

Due to time constraints, the bench testing was carried out within a narrow range of temperature and pressure. It was assumed that temperature would remain within a degree of 38.6°C and that pressure would not change more ±5 mbar during delivery.

During the field trial, recorded temperature inside the cow stayed within the assumed range. Likewise, the pressure of the day stayed within the expected range, however the external pressure experienced at the syringe outlet would have varied from this as it was subjected to movement within the vagina.

5.4 Suggested Enhancements to Current System

5.4.1 Further Testing and Field Trials

To properly quantify the effects of changes in temperature and pressure during delivery, a barometric chamber testing programme would be required. This would establish the robustness of the system under the widest expected range of external pressures and temperatures.

 If another field trial were to be carried out with the opportunity to study two more

variables, external syringe pressure and acceleration vector would be included in the data logging ability.

Logging of external syringe pressure would be used with the barometric chamber results to enable a clearer picture of how the in vivo environment affects delivery accuracy. An algorithm could then be designed to maximize delivery accuracy under these conditions.

The use of a multi-axis accelerometer would allow the logging of acceleration vectors. This would be useful in inferring activity level, mounting behaviour and posture. By validating initial data with human observations, it is hoped that this would enable more accurate heat detection and give an indication of stress levels that the animal feels in different circumstances.

5.4.2 Simple Software Changes

Alteration of the drug delivery profile is straightforward and can be accomplished without specialist training using a text editor. Likewise the following parameters can be altered by modifying a single line of source code and recompiling:

- Data logging period.
- ID transmission interval.
- Safety check pressure, volume, activity and volume limits.
- Resolution of volume dispensed.
- Integrated current to volume dispensed conversion factor.

Without further modification, the system's best use in the medium term is purely as a tool for further research. It can help in understanding the environment in which drug delivery systems must operate in, what they are exposed to and the biological feedback mechanisms it attempts to interact with.

5.4.3 Hardware Changes

The current system can be described as a general computing/communications platform interfaced to specialist drug delivery and monitoring hardware. There is ample capacity for additional computational software and low power hardware requirements in future upgrades.

Beyond the trivial changes mentioned above, hardware/software changes could specialise the existing platform for specific use experiments. In line with this, InterAg are interested in further studies employing the device to measure the pressures in the cow vagina. Currently the DMU only senses pressure inside the syringe for self-diagnostic purposes. The next phase of experimentation will be to add the capability of measuring pressure external to the syringe body.

Other ideas are to:

- Develop a data network and configuration software for in-situ alteration of fundamental drug delivery device behaviour. This includes downloading new delivery profiles and control programs over the wireless link (currently achieved by attaching a wire). This is technically possible given the right software since the microcontroller can re-program its own flash memory over the wireless link.

- Develop a desktop application to plan and download drug regimens and store the results in a database accessible over the company intranet and/or Internet. This is currently achieved by using a variety of off the shelf applications: Drug profiles are altered in a textual format using a standard text editor. A standard terminal program downloads the profiles and retrieves the results. These results are then manually manipulated using a spreadsheet. Integration of these tools into a single application would make it easier to use.

- Utilise the flash memory for data logging. Currently, only 10% of available memory is used because all sensor data is accumulated in RAM only. There is approximately 200K of flash memory that could be used for

additional data logging.

- Inter-Device Range Estimation: Output power is constant over the life of the battery. However, for a fixed distance, some variation of received signal strength is to be expected due to variations in build, component tolerances, placement in the animal and particular propagation effects (such as multi-path fading). There is no direct indication of received signal strength from the transceiver integrated circuit, but received signal strength could be estimated using one of the following techniques:

  - Over-sample the data bits being received. Once the receiver clock has synchronised with the transmitter clock, each sample should be of the same value throughout the duration of the bit period. As received signal strength decreases, the ratio of sampled values within bit periods will approach 0.5.

  - Transmit at different powers with a description of the output power level contained as part of the payload in the data packet. The weakest one to be received successfully can be taken a relative measure of range.

- Replace the RF transceiver board with one based on inductive coupling technology. The LibertyLink product described on page 74 would be ideal (Aura Communications Inc. 2001). The electronics can then be repackaged without the external antenna to make it suitable for a device which has two-way communications and control ability to be located in the rumen.

- Replace the viscous flowing drug vehicle with a gel with allows negligible mixing of the active ingredient at body temperature. Such a gel would allow a multi-drug regimen to be followed using the single, variable rate dispenser currently used. Different solutions are deposited in layers inside the syringe, and to ensure the boundaries between these are clearly defined, a small neutral gel layer is deposited between the active layers. This allows for some inaccuracies in the volume delivered while acting as

a barrier between the active layers to prevent mixing. The layers could consist of solutions containing the same active ingredient, but at different concentrations. Alternatively, they could contain dissimilar drugs, or combinations of both types of layers. Such a system would need careful evaluation in terms of shelf life and storage conditions due to the potential for mixing over time.

- Add bolus capsules to support complex profiles. Spare input/output pads on the DMU printed circuit board (IO1 and IO2) allow the connection of switches to trigger fast acting electrolytic bolus capsules. Bolus shots in parallel with the main controlled release payload can easily be added. A separate and smaller syringe or syringes can be glued inside or outside the body of the Theratron® syringe. A 10% w/w solution of sodium bicarbonate and water is subjected to electrolysis to produce enough gas to deliver 3mL of drug over a period of six minutes. This has been successfully tested in real world conditions.

- Add or modify existing sensors:

  - Multi-axis solid-state accelerometers to allow sophisticated motion detection, posture estimation, path length (by inertial navigation) and inclination (during mounting).

  - Add an external pressure sensor to take into account variations in ambient pressure within the vagina.

  - Global positioning system to track the individual paths of cows. These receivers are now truly postage stamp sized.

  - Digital still camera. A pill-sized ingestible capsule which records colour video images as it travels the GI tract is currently undergoing clinical trials for capsule endoscopy (Given Imaging Ltd 2001). This capsule has already proven that quality images can be obtained with such a small sized, low power device and may prove useful imaging inside the cow. The correct operation of an experimental drug release

mechanism could be verified without resorting to fistulated animals or dissection.

- Add a specialised microphone or vibration sensor with appropriate filtering: Cows coming on to heat are restless and bellow during the 6 to 10 hours before they will first stand to be ridden.

- Electrical-resistance of genital tissues and vaginal mucus. Changes in electrical properties have been observed during reproductive events. Applications for vaginal mucus conductivity include pregnancy checking. In addition, several studies show that electrical impedance in vaginal mucus may be used to pin point proper insemination time (Edwards and Levin 1974, 95:416-420)

- Add biosensors as they become available in a compatible format: glucose, hormone levels, pH etc.

These sensor ideas are mostly speculative and represent thoughts about what might be achieved in the near future. A choice to pursue such a path should only be made after carefully consideration of where effort is best expended since most of these would be expensive and time consuming to implement using currently available technology.

6. Conclusion

6.1 Future Systems

6.1.1 Modification for Other Animals

It is tempting to make assumptions about the direct applicability of any system to work equally as well in other farm animals, however this should be avoided. For example, the method of detecting estrus in cows by measuring peak vaginal temperature works well (Kyle, Kennedy, and Small 1998, 49:1437-1449), but does not apply to sows (Soede, Hazeleger, Broos, and Kemp 1997, 47:245-252). Any applicability to other animals would require careful consideration.

6.1.2 Simplification for Commercial Use

The DMU was designed purely as a research tool without much regard for cost per unit. Various aspects of the DMU could be used as a starting point for development of a cost sensitive device incorporating limited functionality. The gascell monitor IC could easily be replaced by incorporating its function into the microcontroller. The integrating current analogue to digital converter would be replaced by the analogue to digital converter on the microcontroller. A pressure sensor would not be required and the M16C microcontroller could be substituted for a much less expensive one running at a lower speed. Most of the other peripherals would likewise be discarded. The reduced hardware requirement would allow for a much bigger and cheaper battery in the same physical space.

There is a strong argument for eliminating electronics altogether. Complexity should be reduced as mush as possible for cost and reliability reasons. An open

loop gascell operated syringe with controlled release piston and two bolus capsules has been developed by InterAg with this in mind (Rathbone et al. 2001, 50:277-320).

6.1.3 Other Uses for Controlled Drug Release in Farm Animals

Another major application for future controlled drug release products is ectoparasite control. This is a relatively unexplored field due to a perception of it being a less profitable application (Miller 2000, 1:229-249). Even if it is not economic to produce a separate product for ectoparasite control, this represents an opportunity for an adaptable controlled release product to provide both estrus control and parasite control in the one device. There are already separate devices located in/on the ear for estrus and ectoparasite control (respectively). Perhaps a multi-function device for both purposes would provide a competitive advantage since a large part of the cost of deployment of these technologies is the application, monitoring and removal of the devices.

Instead of every animal being subjected to an anti-parasitic drug dose (drenching), the dose would be automatically dispensed if required. Such multi-function devices may require external control after insertion to activate after lying dormant for months at a time. Control signals may be generated as a result of measuring parasite activity. Simpler means may be by manual control over a wireless link whenever the farmer suspects increased risk of exposure, or evidence of infection.

6.1.4 Extension of Cow Communication Ideas

Extension of Social Grouping Propagation Algorithms

A New Zealand patent is pending on the inter-animal communication ideas developed during the course of this thesis (Bunt and Cross 2000, NZ428552). The grouping information can be enhanced with a number of different techniques, three of which are now described:

- Broadcast One-Hop Passive

At regular intervals, each animal asynchronously transmits its ID number to all those around it using a broadcast packet. Those receptions are logged with the payload which contains the time and ID number of the sender. Received signal strength is also logged for each packet. When the animals are next in range of the base station or portable data gathering unit, a central database is updated which provides a master record of all transmissions. The base station has graphing capabilities to visualise which animals were grouped together.

- Polling One-Hop Interrogation

As for Broadcast One-Hop Passive, but transmissions are addressed individually to each animal which has not been heard from recently (within the last 20 minutes for example). Receivers reply to the sender with their ID number. If an interrogation reply is received, they are not interrogated again for another 20 minutes. The sender notes the replies that it gets in the standard manner. The receiver logs the results of all interrogations. Although more complex, this modification more accurately determines received signal strength (since there are two transmissions per exchange along the same path). This reduces the amount of network traffic and increases battery life since close animals are not unnecessarily interrogated.

- Broadcast Multi-Hop Hot Potato

At regular intervals, each animal asynchronously transmits its ID number to those

around it. Those receptions are logged with the payload containing the received signal strength, time the original packet was transmitted and ID number of the originating animal. The ID number of the receiving animal is appended to the data, and it is rebroadcast after a time delay based on the ID number of the receiving animal (so that collisions do not occur with other animals responding in the same way). If an animal receives a packet and it sees its own ID in the payload, it does nothing. This prevents data packets from continually circulating throughout the herd. This data is of the same quality and can be processed in a similar manner as with the one-hop passive technique. The originator also logs any of the forwarded packets that originated from itself for another estimation of animal grouping. The packet may take one of several paths, or even arrive via multiple paths to a given animal. Only the first packet to arrive is processed if there is a command present, but the signal strengths of any subsequent packets are logged. The rate of transmission is reduced during the night to conserve battery power.

Contagious Model of Vaccination Delivery

While the experimental results presented earlier demonstrate a simple form of communication useful for determining social grouping, there are many other areas of potential application.

There is an interesting parallel between the spread of information by inter-cow communication and the action of a contagious disease. Imagine that a multi-drug delivery device exists and is present in each animal. This device contains, as one of the available drug types, a vaccine which is effective for a particular disease. There are disadvantages to applying the vaccine so it is never applied unless absolutely required (e.g. the vaccine for foot and mouth disease). However, for it to be effective, it must be applied before exposure. Now, when the ID number of a cow is transmitted to other cows around it, a flag indicating exposure to the disease is sent with it. If an ID with that flag set is ever received, it activates the specific vaccine dose and propagates that same flag to others around it. Only the original animal needs the flag set by the detection of the infection. The flag could be set by automatic means, or manually over the wireless link.

In essence, the spread of vaccine deployment exhibits biomimicry with respect to the contagious disease, but is configured to be slightly more contagious, resulting in "just in time vaccination". The example of a contagious disease has been used here, but this method could equally apply to other situations where the organism is airborne, or spread by some other proximity based distribution model.

6.2 Extending the Control Loop to the Organism

6.2.1 Measuring Control Factors in the Organism

Previously, it was stated that a closed loop control system provided the means for accurate volume and rate delivery in the DMU. However, this closed loop encompasses only the drug delivery mechanism itself. A more sophisticated approach would include the organism in the control loop. This requires measuring one or more control factors in the animal.

In the present case, progesterone level in milk or blood would provide the most appropriate feedback information if progesterone was being delivered. Rather than simply define the delivery profile by the rate at which progesterone exits the syringe, it could be defined instead by the level in the animal. This would allow more efficient use of the drug payload and provide a more targeted approach which partially includes environmental factors. More frequent sampling and finer control of the delivery rate leads to greater reliability and less side effects because only the minimum amount of drug need be delivered (Mason, Linkens, Edwards, and Reilly 1996, 13:243-252).

Progesterone levels in the animal are influenced not only by the amount delivered artificially, but also by naturally occurring levels in the animal (Webster 1993, 2), which is in turn dependant on a variety of external factors. These factors include diet, extremes of weather, age, calving history, general condition, and predominantly, the current point in the estrous cycle.

There are two main barriers to such an approach. The first is the difficultly of

sensing useful levels of the desired control signals. At present, there is no easy way to sense hormone levels with a remote embedded device that is sensitive, easy to integrate, durable and non-intrusive. Instead, the routine approach is take a blood sample with a needle and send it to a laboratory.

The second barrier to developing a control system which includes the organism is the added complexity of device/animal interaction (Hacisalihzade 1989, 9:44-45). Rates of delivery in terms of mL/day are immediately understood and easily verified. By contrast, a control loop involving the animal requires a deeper level of understanding of the animal itself and a mathematical model of the transfer function for the actuator/feedback path. Further, it is unlikely that the end goal of the drug regimen can be quantified with only one measured variable — biological systems are rarely that simplistic. Instead a multi-variate control system would be required, implying a still greater investment in sensor technology and understanding and modelling of the biological system.

Such a system would find it difficult to produce an acceptable result under all of the exceptional conditions met in the real world and this might explain why few systems ever reach the stage of formal clinical evaluation (Mason, Linkens, Edwards, and Reilly 1996, 13:243-252). Applications such as drug infusion for atracurium-induced muscle relaxation for eye and brain surgery are safety-critical, demanding a robust and reliable solution which at present is not well developed. Another example is the recent work on a closed loop drug delivery system to maintain cardiac output at set point range for congestive heart patients. Again, although said to be promising, this has not been transferred through to a physical realisation with formal clinical evaluation (Shah, Bekker, and Reisman 2000:49-50).

So although externally operated biomedical machine/human closed loop control systems are routine for many applications, including anaesthesia (Linkens and Abbod 1998, Digest No. 1998/514:2-1-2/4), totally embedded solutions for drug delivery are in a comparatively early stage. No doubt embedded closed loop drug delivery systems for safety critical systems will be successfully developed. Hope can be found nearby in the success of similar closed-loop technologies which are

employed in safety critical functions. Although not drug delivery devices per se, internal pacemakers which include some form of automated defibrillation are notable. These devices prove the immediate benefits for the patient in developing such embedded, portable systems.

The effort involved in discovering and applying the much needed application specific knowledge can be justified on a number of additional grounds. Assessing the behaviour of the actual device/animal interaction and comparing it to the model would lead to a greater understanding of the biological system under consideration.

6.2.2 Measuring Control Factors from Excretions

Instead of placing the measuring apparatus in the animal, an indication of internal status can be provided by animal excretions. This greatly simplifies the need to handle the animal or subject it to implantation of devices. Faeces and urine are example of excretions which have been used to determine the presence of various chemical states within the cow. Some promising work has been carried out which gauges the stress level and general health from examining the ketone levels in the cow's breath.

These herd based systems would provide individual and collective data to a remote computer. Integration with herd management software would close the control feedback loop, allowing the devices to be controlled over the Internet

A more practical excretion for a production unit is the on-line testing of milk — the advantage being that it is already collected from the dairy cow for its intrinsic value. By monitoring for blood, somatic cell count, percentage solids and other factors, an automatic treatment response could be carried out. For example, a high somatic cell count may indicate mastitis, prompting the milking parlour management computer to automatically deliver anti-biotic treatment. This is an over simplified example, and such a treatment would not be possible given this amount of information, but it illustrates the general principle of what might be possible in future once more information is being collected from each milking on a routine basis and can be applied to automated controlled release drug delivery

systems. Other applications include the automated release of drugs to control ectoparasites.

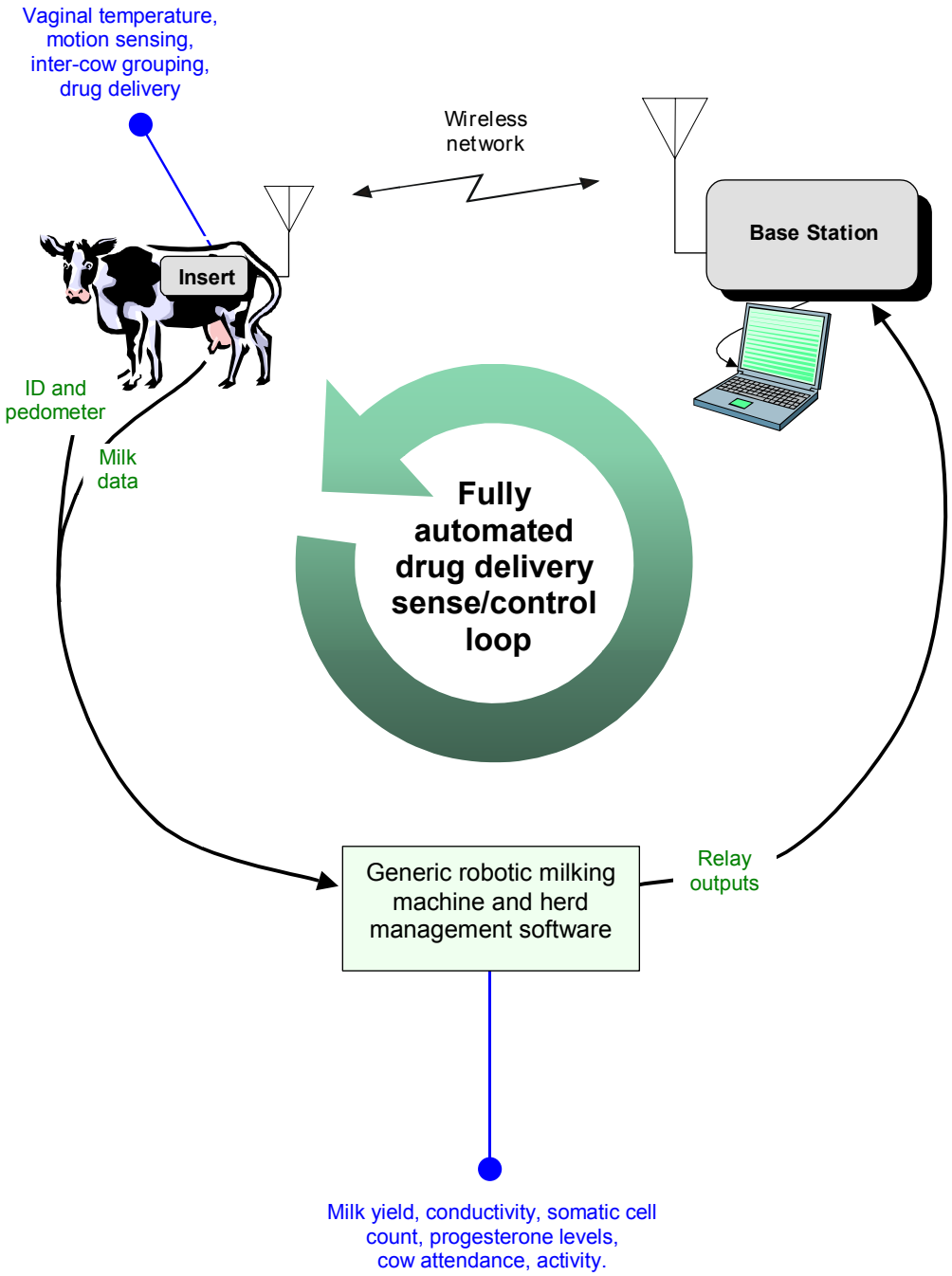

Vaginal temperature, motion sensing, inter-cow grouping, drug delivery
Wireless network
Base Station
Insert
ID and pedometer
Milk data
Fully automated drug delivery sense/control loop
Generic robotic milking machine and herd management software
Relay outputs
Milk yield, conductivity, somatic cell count, progesterone levels, cow attendance, activity.

Figure 46: Closed Loop Drug Delivery
(Claycomb 2001)

A limited form of feedback is already a part of commercial reality in the Fullwood

Ltd. robot milking system (Fullwood Ltd. 2001b;Fullwood Ltd. 2001a). The Merlin robot milker and others like it account for 30% of new milking system installations in the Netherlands.

Each cow wears an ID tag and pedometer. When the cow feels like being milked, it approaches the robot which dispenses the calculated amount and type of feed based on its accumulating database of statistical information about that particular cow and how it is performing relative to the rest of the herd. On-line sensing of the milk is limited to conductivity, flow and volume per quarter at this stage. If the robot senses the cow is sick (e.g. significant drop in activity level due to lameness) she is automatically directed by separation gates to an isolated pen for examination by the farmer when he arrives.

Such machine/cow feedback is limited at this stage. The software operates the robot and reports on feeding, milk quality, milk yield and estrus detection (through activity level). At the moment, the farmer makes most of the decisions, but as on-line sensing and drug delivery technology improve, more and more of the decision making will happen under autonomous control, rather than human intervention.

Figure 46 depicts a situation where a such a milking robot and herd management software might communicate with a drug delivery device inserted inside the cow (Claycomb 2001). The insert and base station could be an extension of the DMU and base station developed for this thesis. Thus, the individual elements of such a system already exist in working form. To realise the system in the diagram requires only system integration and testing.

6.3 Remote Data Gathering From Many Sites

At present, information is obtained by addressing each animal on a manual basis. To totally automate the process, a network of information gathering sites could be built. The transponder in each cow would be interrogated by a base station placed in a position such that each cow comes within adequate range often enough for the

system to be of use. The typical range is 30m so a base station placed inside a milking shed for a milk-producing herd would be ideal. The base station can also be made portable if required.

Looking at one system installed on a farm as a whole, it can be symbolised as follows.

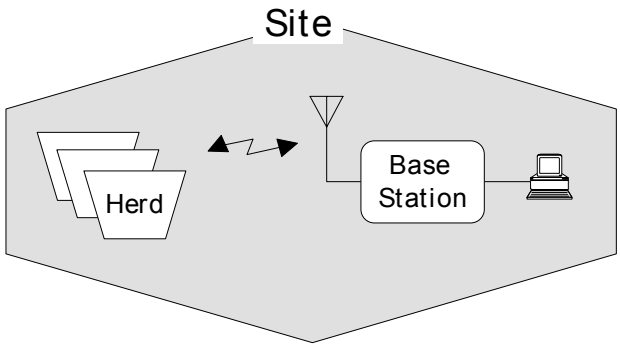


Figure 47: Symbolisation of One Monitoring Site

The base station periodically asks if any transponders are in range. If so, it determines if any need servicing, and then asks those requiring service to respond in turn. Results such as those already achieved by the DMU are recorded in the local database for each cow.

The base station in this set up is not very intelligent, and is essentially only an interface to the controlling program and database on the nearby personal computer that makes all of the important decisions. The connection to the telephone network enables an exchange of information from the farm to a database located remotely. Results are sent each day to the drug programme administrator via this link.

It also allows changes to the drug programme to occur without requiring a visit to the farm. For example, it might be that a trend develops in the results that are collected over the first week, and the drug programme administrator wishes to change the rule-based system present in the DMU within the cow. This can be accomplished by the same two-way link.

The secure and robust drug delivery process has many parallels with financial transaction processing networks used in such applications as automatic teller

machines. In such cases, reliable communication of authentication, requested action and acknowledgement of completed tasks must be carried out with high reliability. System reliability, security and robustness would be key features of further development.

If we add more farms to the drug trial, they can all communicate via the Internet to the sponsor's local area network for centralised recording, feedback, control and monitoring:

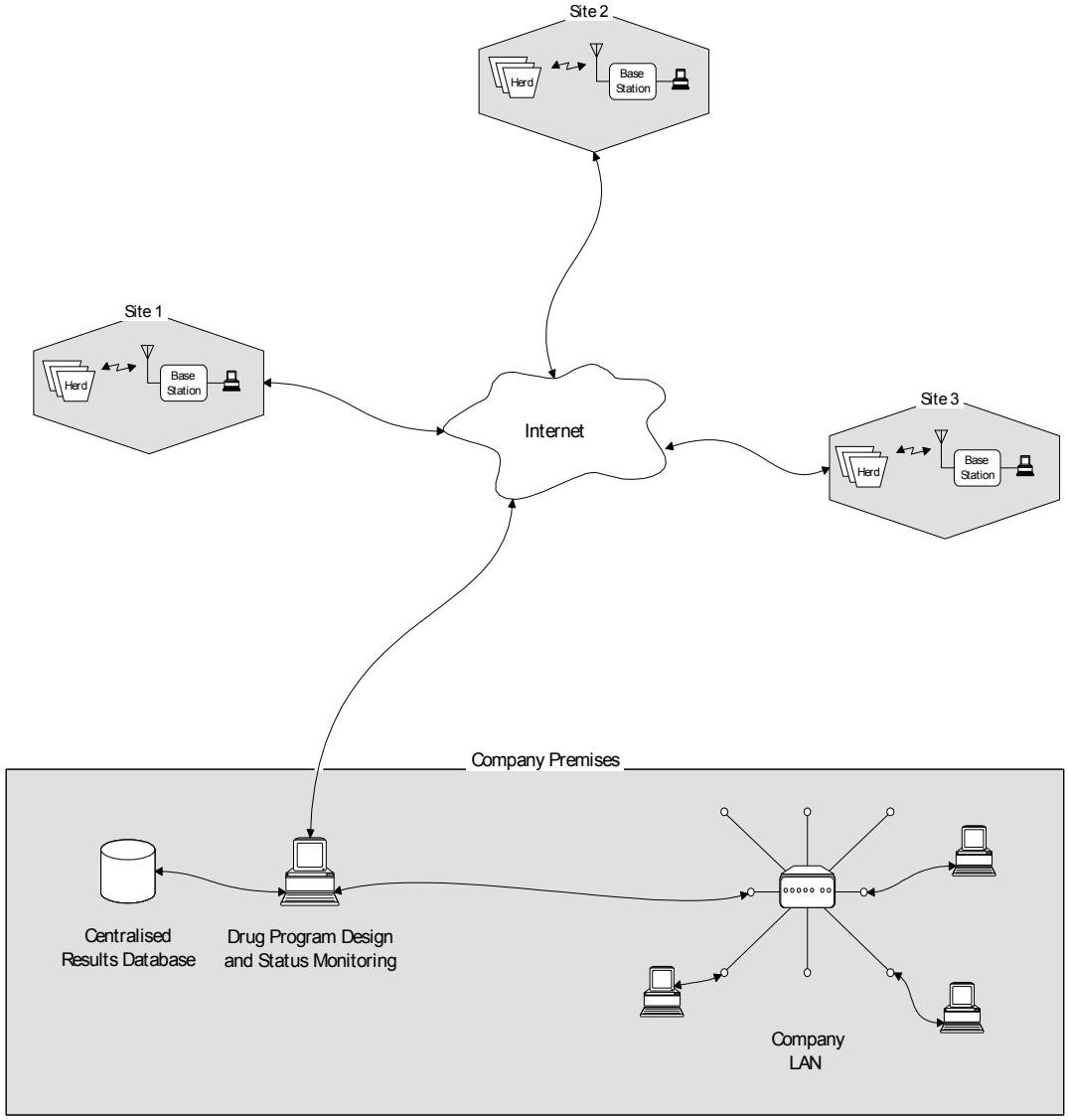


Figure 48: Network for Remote Design and Monitoring of Drug Delivery Programmes

Normally, the results would be sent once a day from each active farm to the drug programme administrator's central database on the sponsor's premises. Any pending reply or system status enquiries could be made at the same time. This would take about 10 minutes per farm and occur automatically in the early hours of the morning for least disruption to farm activities.

Procedures on the farm could be controlled remotely. For example, the central monitoring drug programme administrator might be in Hamilton, New Zealand. If a serious problem developed in a site somewhere in Australia, all remaining sites in the world could be told to suspend drug deliveries until further notice. This detection and control function could be set up to happen without local human intervention.

There would be some time delay due to the fact that DMU needs to be transported by the cow back within range of the local base station before the command can take affect. If this was a problem, a repeater system could be deployed to extend the range of the DMU communication range to the entire farm. A system of farm wide cow-to-base-station communication already exists in a simplified one-way form. The commercially available HeatWatch® system from DDx Inc, mentioned previously, transmits mounting activity for estrus control via repeaters in 300m hops to the farmer’s computer.

6.4 Integrated Estrus Detection

No single method of estrus detection is 100% reliable. Exhaustive visual observation, ultra-sound, rectal palpation and blood sampling for hormone levels are the best methods in terms of detection and rate, but are not practical for the average dairy production unit due to their significant cost. You have to go a long way to beat tail paint backed up with a quick knowledgeable observation and a notebook.

To automate the estrus detection problem for production units with low-skilled workers and a high cow/worker ratio, other methods must be employed.

However, there are no commercial products exist that have met wide spread adoption as being adequately accurate and economical.

Single sensor solutions are prone to error:

- Temperature increases occur with estrus, but other influences also affect temperature to such a degree that it makes temperature sensing by itself unreliable.
- Tail head pressure sensing devices are susceptible to false triggering when the cow lies against a fence.
- The use of motion sensing detectors is cow specific, varied with footing conditions and does not detect silent heat.
- Electrical resistance has a high variability between cows and is not reliable by itself.

In short, no one method has been successful enough to make the wide spread use of estrus detection devices economically viable.

There is a gap in the market, for an integrated form of estrus detector with an integrated package of sensors that can look at all the indicators to produce a more reliable result. The challenge is one of cost; manufactures must be able to convince dairy farmers that these systems will pay for themselves in terms of initial outlay and maintenance.

The attributes of a successful future system would be:

- Integrated animal ID, temperature, conductivity, motion and pressure switch mounting sensors.
- Intelligent enough to process the combined data for that cow.
- Low cost/low maintenance.

Other attributes would be desirable but might not be worthwhile in the cost/benefit stakes. This includes the ability to communicate to the remote

database for herd management.

To sense mounting, the device must be located at the tail head. To sense mucus conductivity, probes must be inserted into the vagina. A system could be attached to the tail, HeatWatch® style, with probes lodged in the vagina. There are many practical difficulties however, not the least of which is the attaching line being snagged or pulled out by other curious cows. A short range radio link would work and has worked well to solve a similar problem for a human pedometer system called FitSense FS-1. This system has a shoe/watch wireless link and uses an accelerometer for a simplified inertial navigation to calculate path length (FitSense Technology 2001). It uses a radio frequency IC from the same family as that used in the DMU.

No doubt these ideas are already under evaluation for commercial development, but cost is the biggest barrier. Perhaps estrus control is too narrow an application for all of this technology to be deployed at once. The inclusion of an ID function is good example of how extra value can be included for little extra cost per cow to make some form of cow mounted information appliance a viable platform.

6.5 Conclusion

6.5.1 All Objectives Completed

Advances in cow estrus detection and synchronisation via controlled drug release can provide efficiencies in the dairy industry. Electronic control and monitoring of intravaginal delivery in farm animals can help meet this need. The objectives of this thesis emphasised the need for an intelligent communicating device with the capability to:

- Precisely control a variable rate delivery profile.
- Provide external control of the delivery system.
- Monitor the animal and delivery process.

A programme of design, construction, testing and experimentation proved the technical feasibility of such a system. External control and monitoring of drug delivery in farm animals was successfully carried out in a week long trial with five cows. Methods, problems and solutions involved in developing and using the system were described. Original experimental results were:

- Social grouping determined by inter-cow wireless communication.
- Precise delivery of a pharmaceutical vehicle over a short or extended period of time in accordance with a complex profile. This was to an accuracy of three percent under controlled conditions, or seven percent in real world conditions in vivo.
- External wireless control/override of drug delivery in the cow. Normal and external controlled delivery subject to safety limit override criteria.
- The ability to gather an array of environmental data at once from the cow vagina by wireless communication.

6.5.2 All Initial Design Criteria Met or Exceeded

System performance was assessed and found to meet or exceed all initial design criteria. Attention was paid to contemporary controlled release mechanism design philosophy. The system exceeded the initial design criteria in the following areas:

- Real world in vivo accuracy of 7% was better than the required accuracy of 10%.
- Range of communication was up to 60m line of sight, compared to the required 30m.
- Battery life was seven weeks, greatly exceeding the three week requirement.

6.5.3 Future Work

Possible improvements to the existing system were noted. These included improvements in mechanical reliability, alteration of the software to support longer term data gathering and the ability to dispense more than one drug. The multi-drug variable rate, serially delivered, platform would support complex protocols and be able to dispense bolus shots in parallel with the main controlled release payload.

Future systems may extend the control/feedback loop outside the drug delivery device, the animal itself, and perhaps even the farm at which the animal resides. These herd based systems would provide individual and collective data to a remote computer. Integration with herd management software would close the control feedback loop and allow interaction with the devices over the Internet while they are in the cows.

6.5.4 Summary

This thesis demonstrated the feasibly of external control and monitoring of drug delivery in farm animals. The development programme produced a practical device which met or exceeded all initial design criteria in real world conditions, generating four significant and original results.

The Delivery and Monitor Unit is a valuable tool for further research into drug delivery in farm animals.

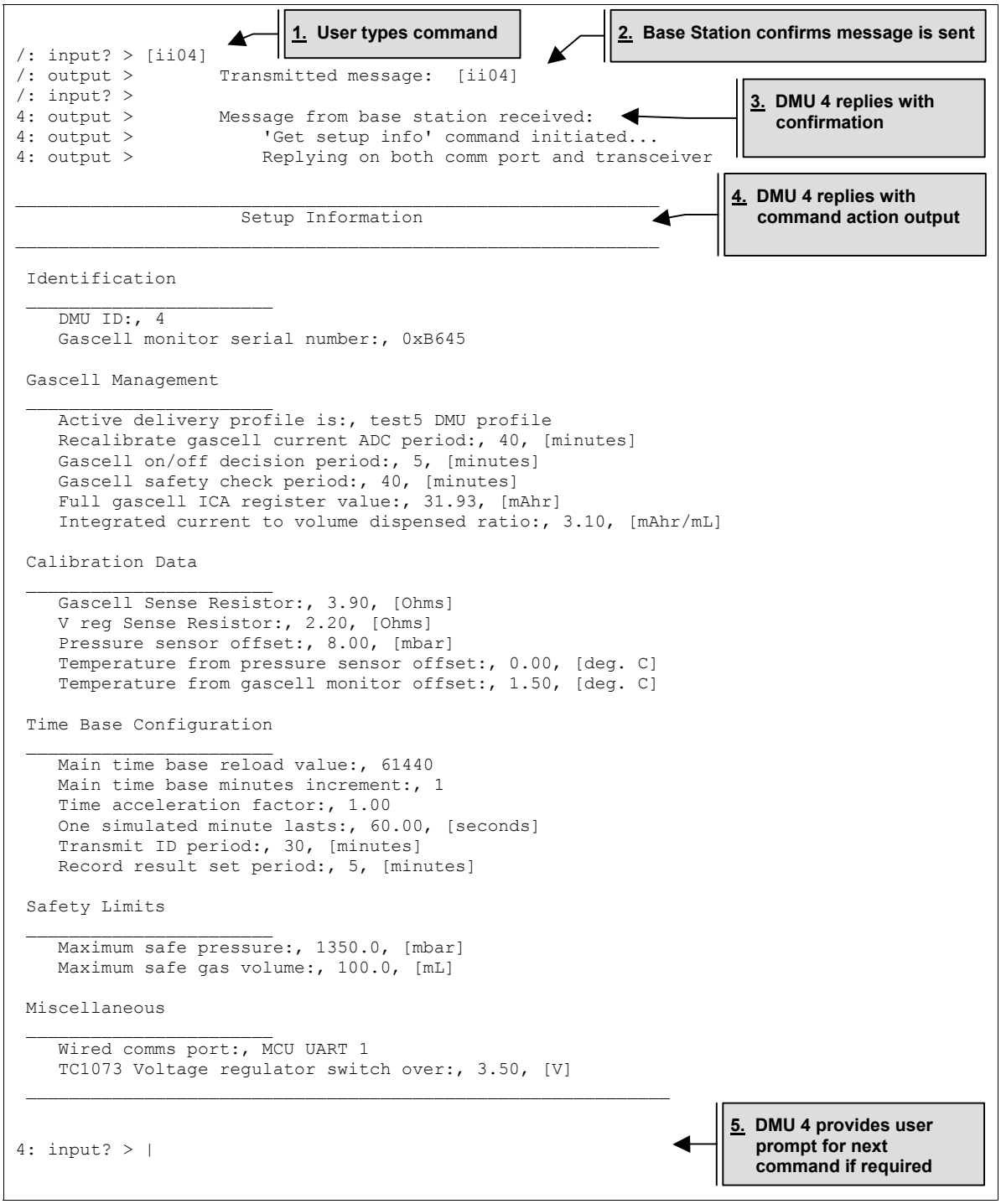
Appendix A: Additional Experimental Results

Table 8: Description of Observations, Results and Manipulations for DMU 3 and Control Syringe

Date/Time	Day of Trial	Time Since Reset	Time Since Pres-surisation	DMU 3 Observed Piston Position	Actual Volume Delivered from Piston Position	Estimated Volume Delivered by DMU from Integrated Gascell Current	Control Syringe Piston Position	Gascell Control	Comments
dd-mm-yyyy: hh:mm	Day	min	min	mm	mL	mL	mm		
22-5-2001: 1755		0	-191	58	0.0		60		Piston start position at power on reset
2155	-1	240	49	63	0.0	0.5	60	As per programmed delivery profile.	Pressurisation complete. Pressure is decreasing to minimal after initial pressurisation so some extra leakage will occur. The vehicle delivery programme started 49 minutes previously.
23-5-2001: 0700	0	785	594	64	0.7	2.0	60	As per programmed delivery profile.	Two hours before insertion. This does not accurately reflect the exact piston position just after insertion because the change in temperature causes a change in volume and the piston will move slightly.
0940		945	754						Insertion in to cow.
24-5-2001: 0715	1	2240	2049					As per programmed delivery profile.	Could not download.
25-5-2001: 0911	2	3795	3604	81	12.0	10.2	Not measured	Gascell forced off	Download accomplished. Taken out, measured, put back in override: switched gascell off
26-05-2001: 0730	3	5160	4969					As per programmed delivery profile.	Download accomplished. Override made inactive.
27-05-2001: 0730	4	6555	6364					Gascell forced off	Download accomplished. override: switched gascell off
28-05-2001: 0845	5	8100	7909	90	18.0	19.2	61	Gascell forced off	Download accomplished. Taken out, measured, put back in override: switched gascell off
29-05-2001: 0845	6	9555	9364					As per programmed delivery profile	Download accomplished. Override made inactive..
30-05-2001: 0845	7	10985	10794	102	26.0	30.0	66	As per programmed delivery profile	Download accomplished. Out for good. Piston position inaccurate because DMU 3 fell out of the cow at 1800 the previous day and may have been subject to rough treatment.

mm to mL conversion factor [mL/mm]: 0.6667 Time at pressurisation [min]: 191

Table 9: User Requesting Setup Information From DMU 4 Over Wireless Link


1. User types command
2. Base Station confirms message is sent
3. DMU 4 replies with confirmation
4. DMU 4 replies with command action output
5. DMU 4 provides user prompt for next command if required

```
/: input? > [ii04]
/: output >        Transmitted message:  [ii04]
/: input? >
4: output >        Message from base station received:
4: output >            'Get setup info' command initiated...
4: output >            Replying on both comm port and transceiver

_____________________________________________________________
                    Setup Information
_____________________________________________________________

 Identification
 ______________________
    DMU ID:, 4
    Gascell monitor serial number:, 0xB645

 Gascell Management
 ______________________
    Active delivery profile is:, test5 DMU profile
    Recalibrate gascell current ADC period:, 40, [minutes]
    Gascell on/off decision period:, 5, [minutes]
    Gascell safety check period:, 40, [minutes]
    Full gascell ICA register value:, 31.93, [mAhr]
    Integrated current to volume dispensed ratio:, 3.10, [mAhr/mL]

 Calibration Data
 ______________________
    Gascell Sense Resistor:, 3.90, [Ohms]
    V reg Sense Resistor:, 2.20, [Ohms]
    Pressure sensor offset:, 8.00, [mbar]
    Temperature from pressure sensor offset:, 0.00, [deg. C]
    Temperature from gascell monitor offset:, 1.50, [deg. C]

 Time Base Configuration
 ______________________
    Main time base reload value:, 61440
    Main time base minutes increment:, 1
    Time acceleration factor:, 1.00
    One simulated minute lasts:, 60.00, [seconds]
    Transmit ID period:, 30, [minutes]
    Record result set period:, 5, [minutes]

 Safety Limits
 ______________________
    Maximum safe pressure:, 1350.0, [mbar]
    Maximum safe gas volume:, 100.0, [mL]

 Miscellaneous
 ______________________
    Wired comms port:, MCU UART 1
    TC1073 Voltage regulator switch over:, 3.50, [V]
 ____________________________________________________________


4: input? > |
```

Appendix B: DMU Schematics

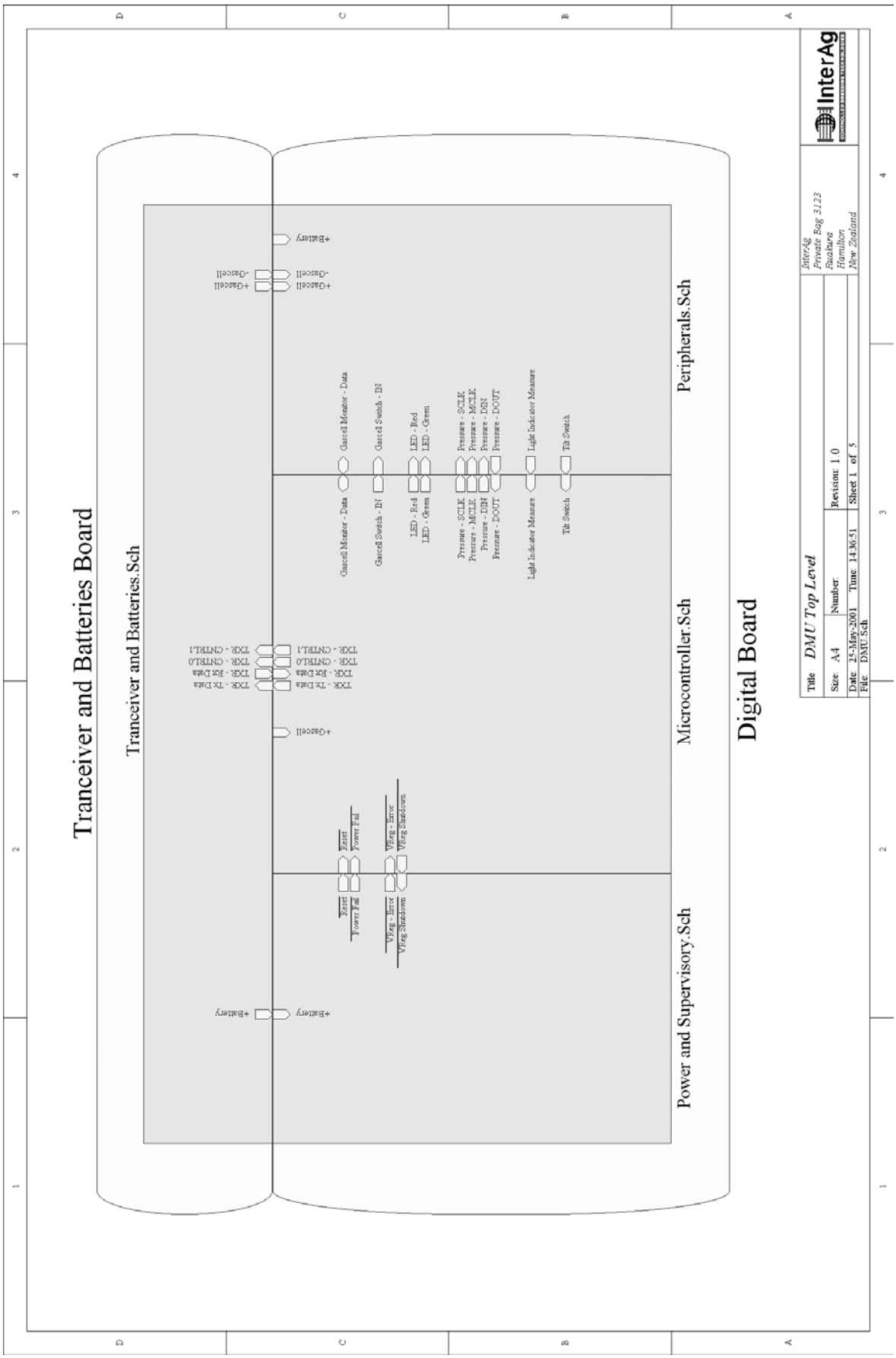


Figure 49: DMU Schematic: Top Level

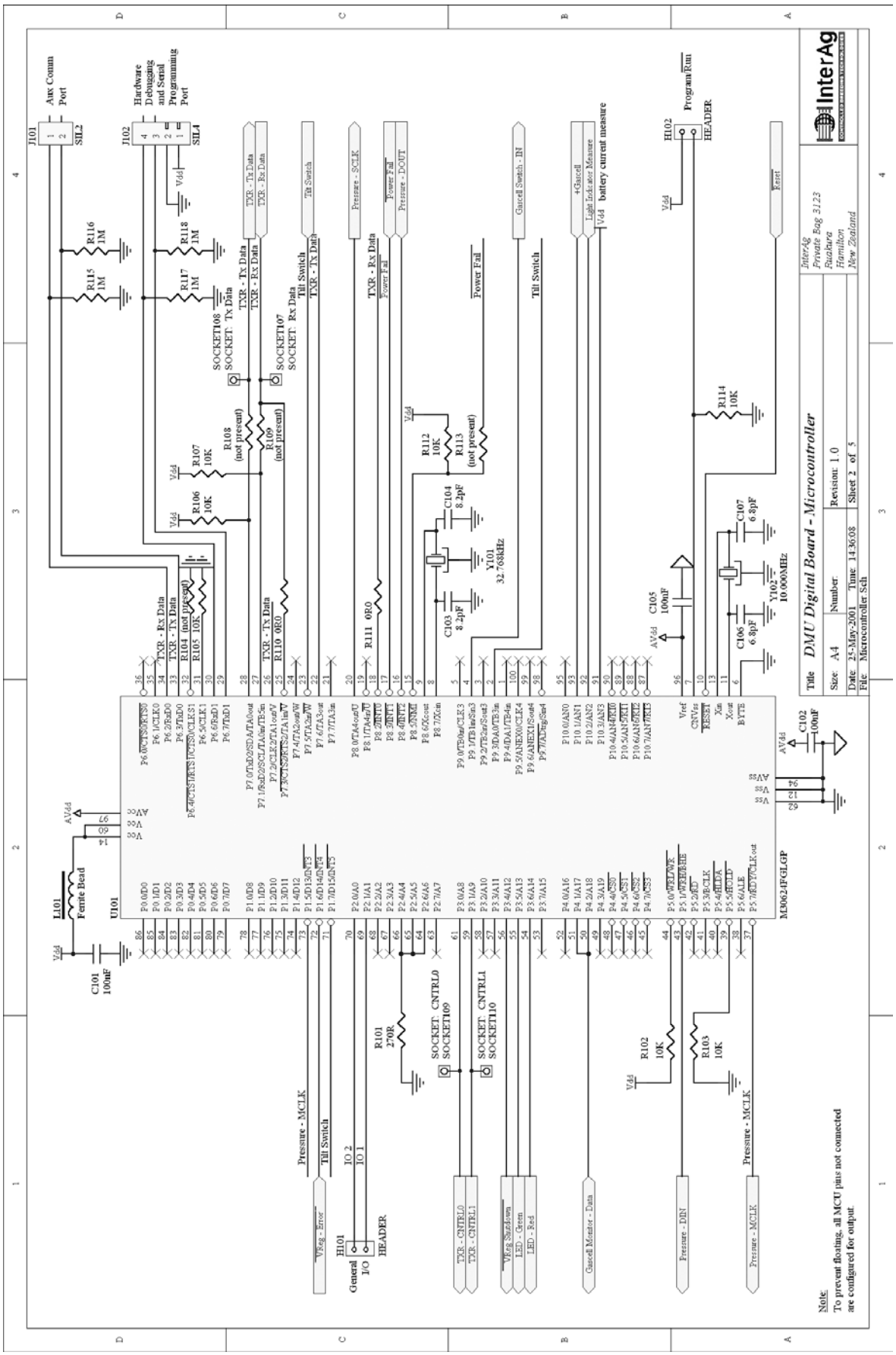


Figure 50: DMU Schematic: Digital Board — Microcontroller

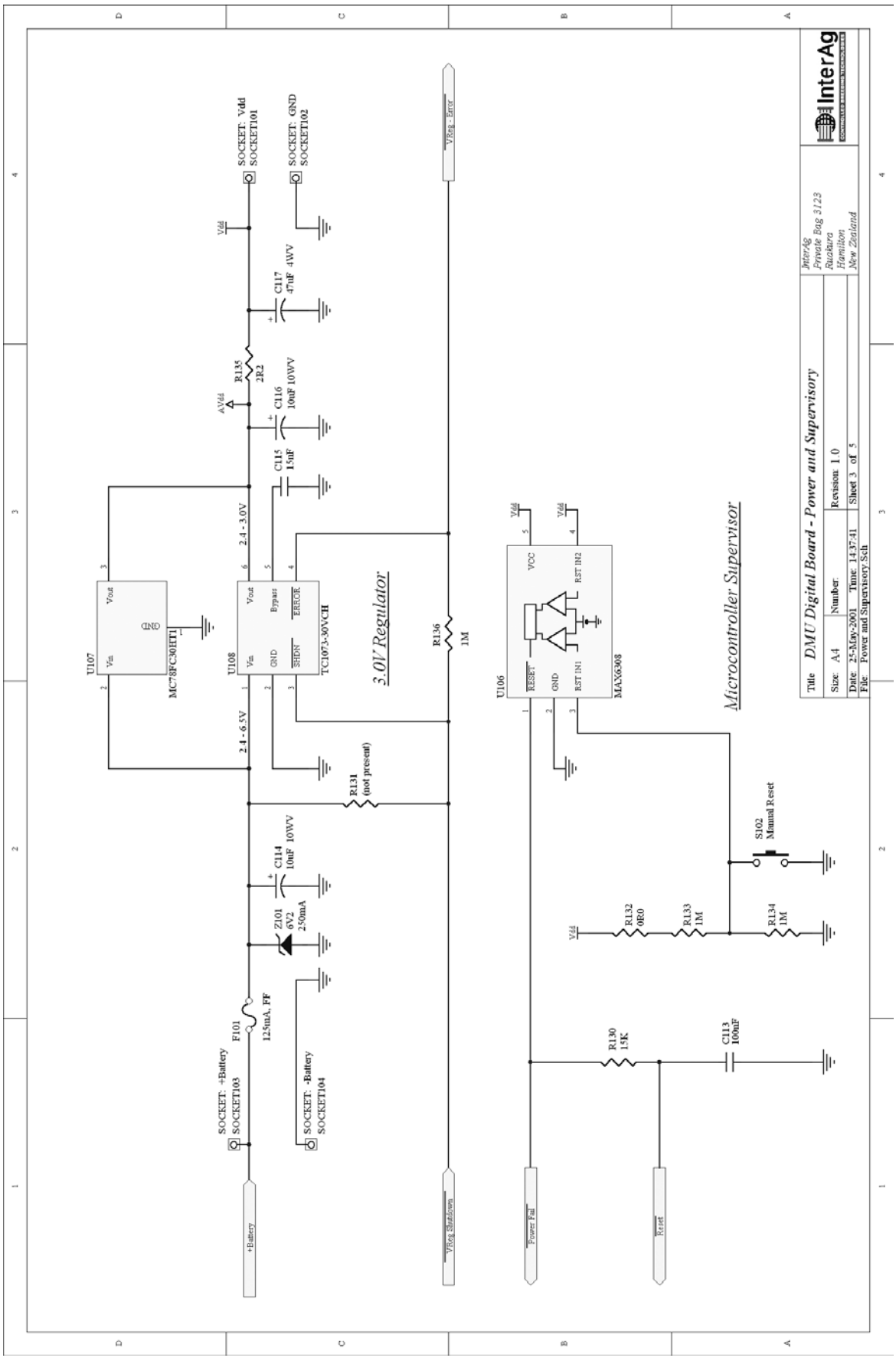


Figure 51: DMU Schematic: Digital Board — Power and Supervisory

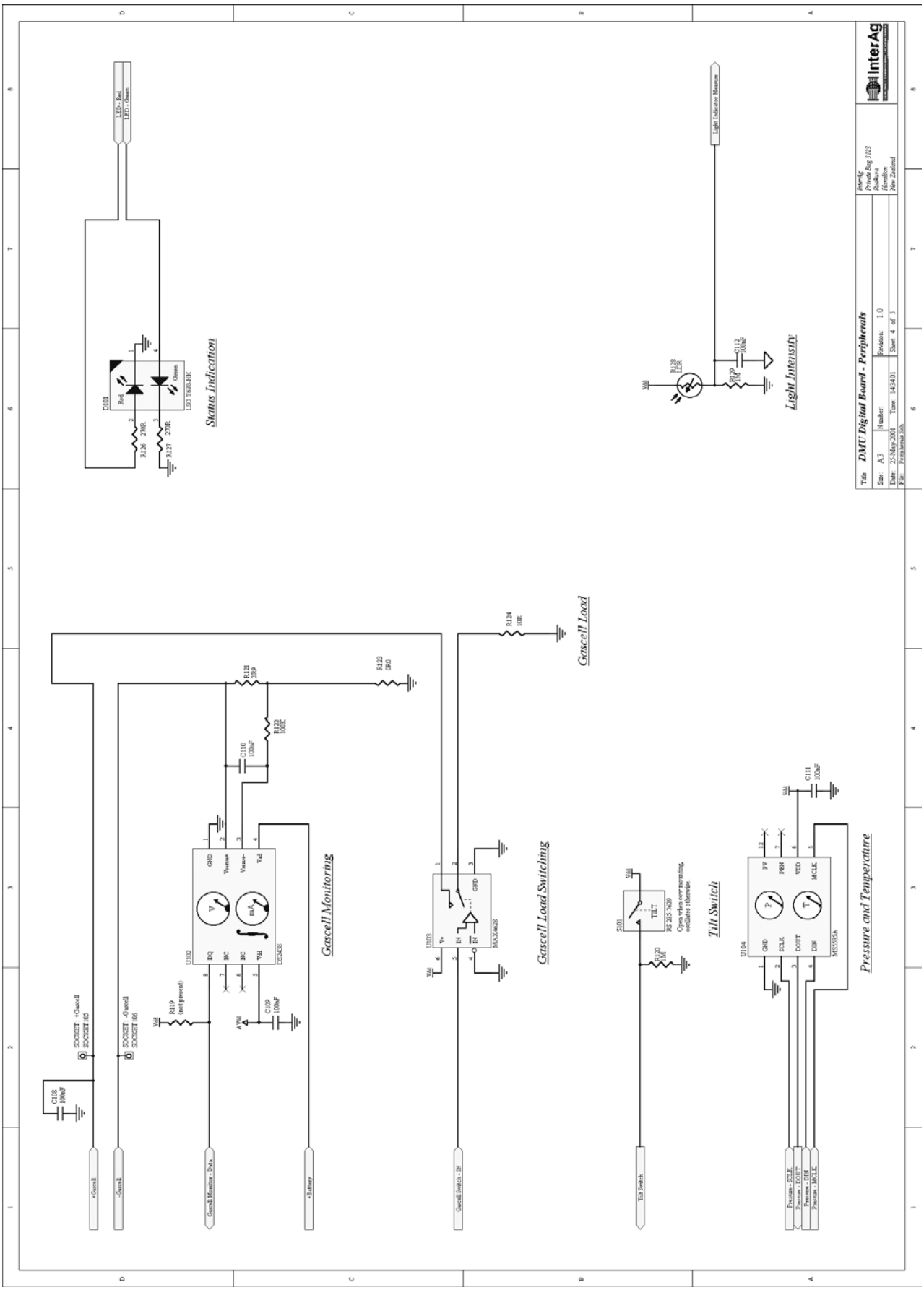


Figure 52: DMU Schematic: Digital Board — Peripherals

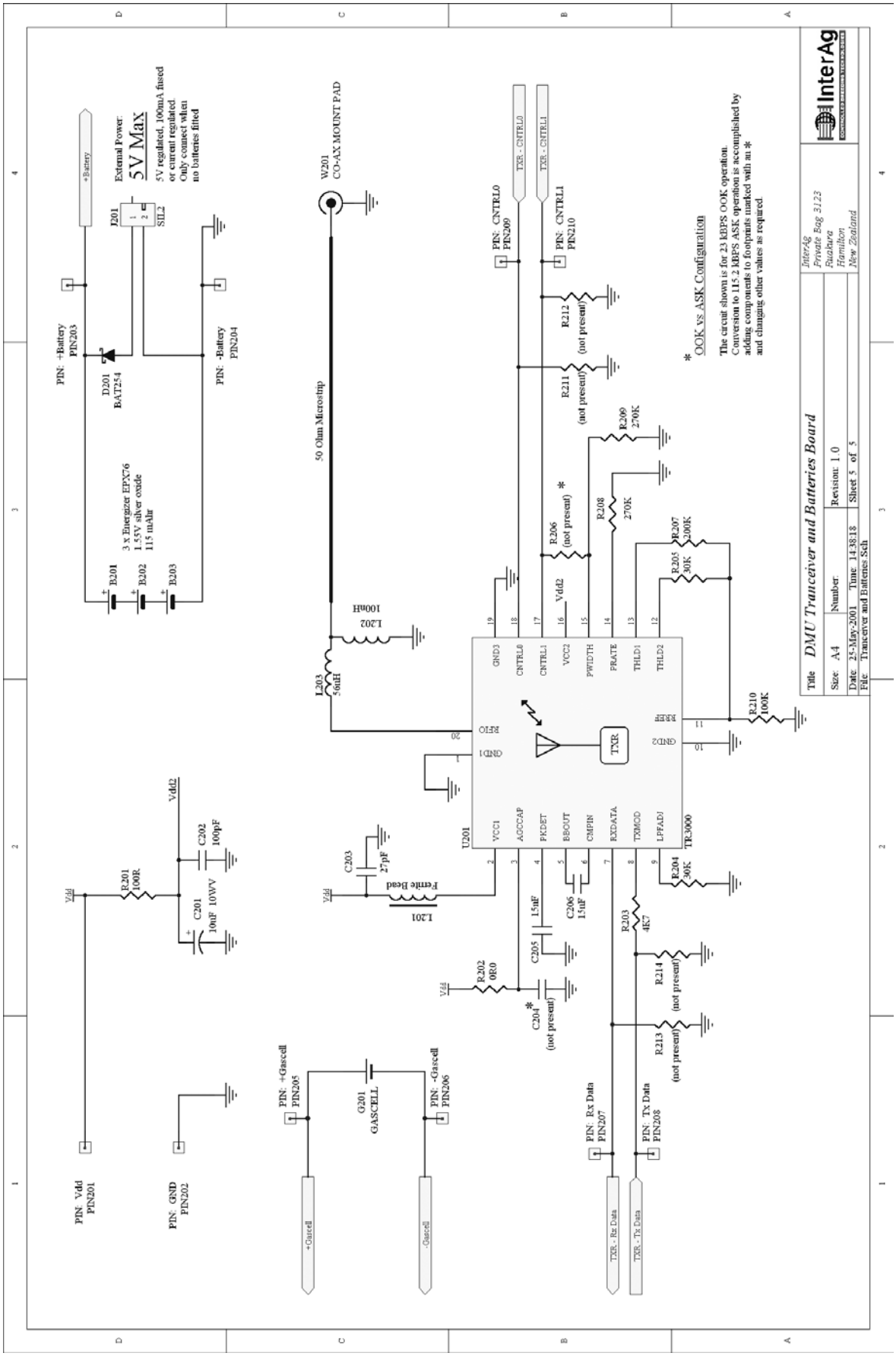


Figure 53: DMU Schematic: Transceiver and Batteries Board

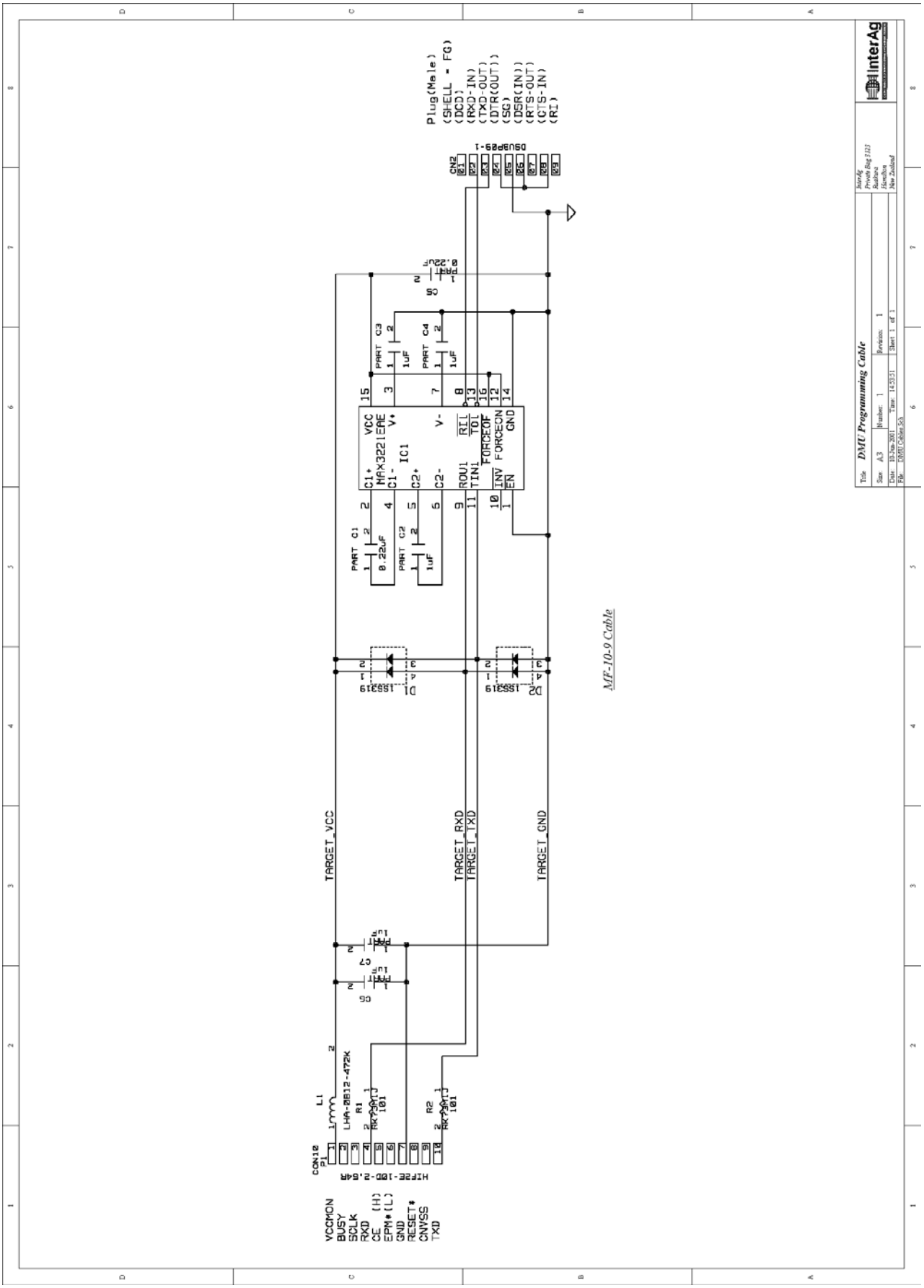


Figure 54: DMU Schematic: Programming Cable

Appendix C: DMU PCB Layout

Table 10: DMU PCB Specifications

Item	Description
Layers	Six conductive layers: Top and bottom signal layers, inner layers 1 and 2, power and ground planes. Solder mask both sides, no silk screen.
Substrate	Core: FR4 fibreglass, 1.8mm. Pre-preg 1080 and 7628 grain.
Design Rules	Minimum clearance: 7 thou Minimum track width: 7 thou
Dimensions	Circular: 28.6mm diameter
Fabrication	Solder mask over bare copper with plated through hole vias and holes. Hot air, solder levelled finish. Full net test.

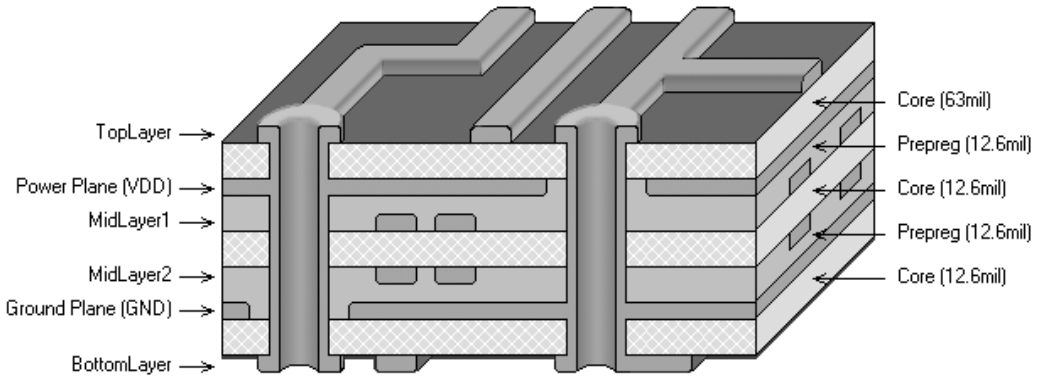


Figure 55: DMU PCB Layer Stack Up

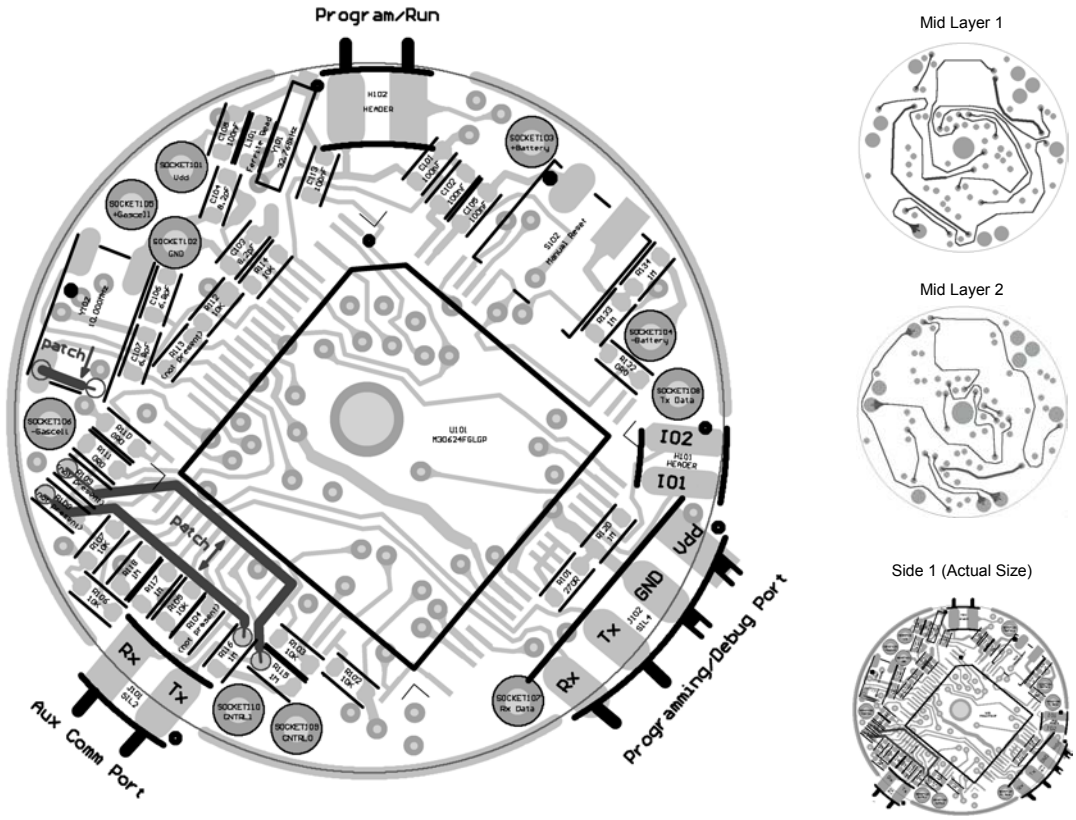


Figure 56: DMU PCB Layout: Digital Board Side 1 and Inner Layers

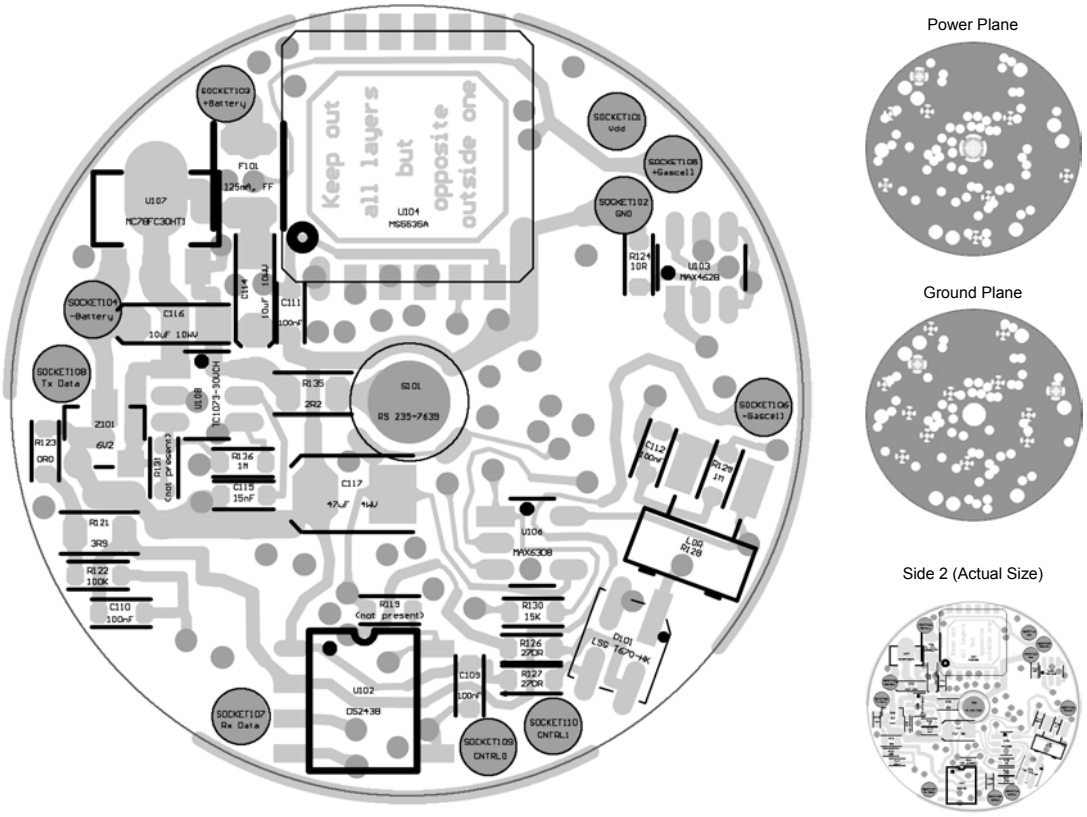


Figure 57: DMU PCB Layout: Digital Board Side 2, Power and Ground Planes

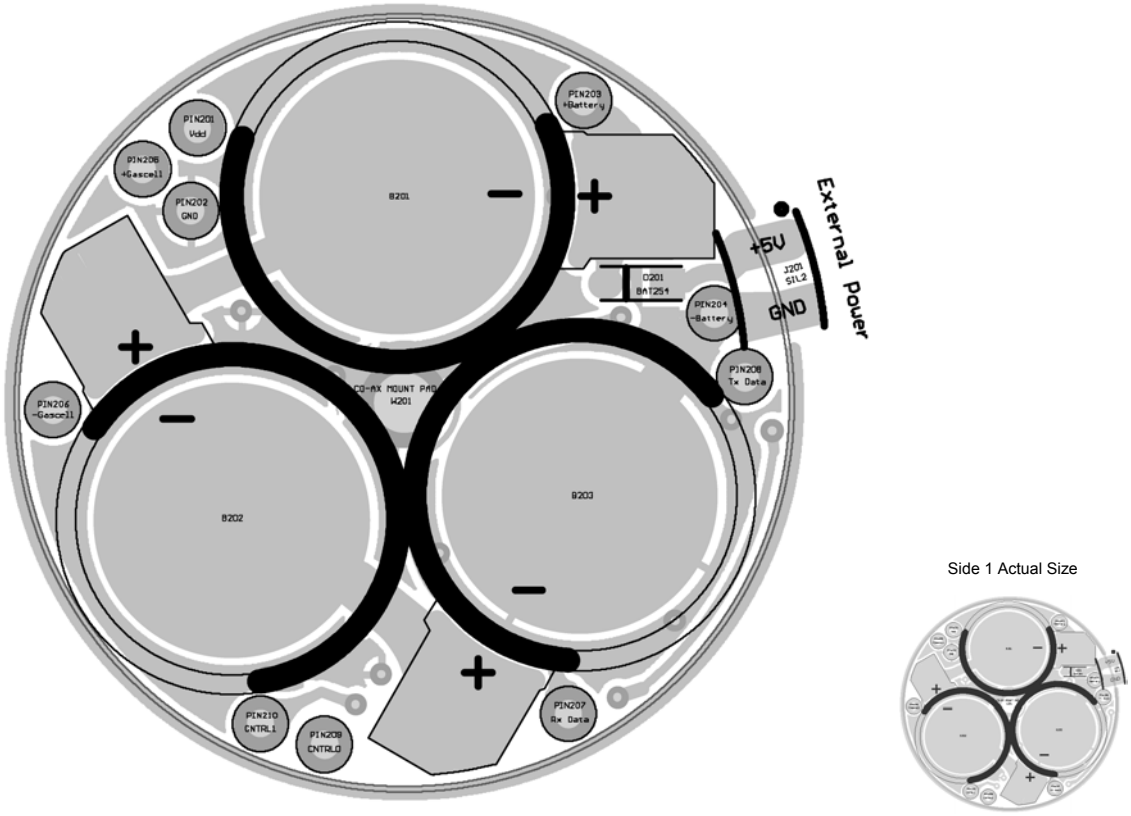


Figure 58: DMU PCB Layout: Transceiver and Batteries Board Side 1

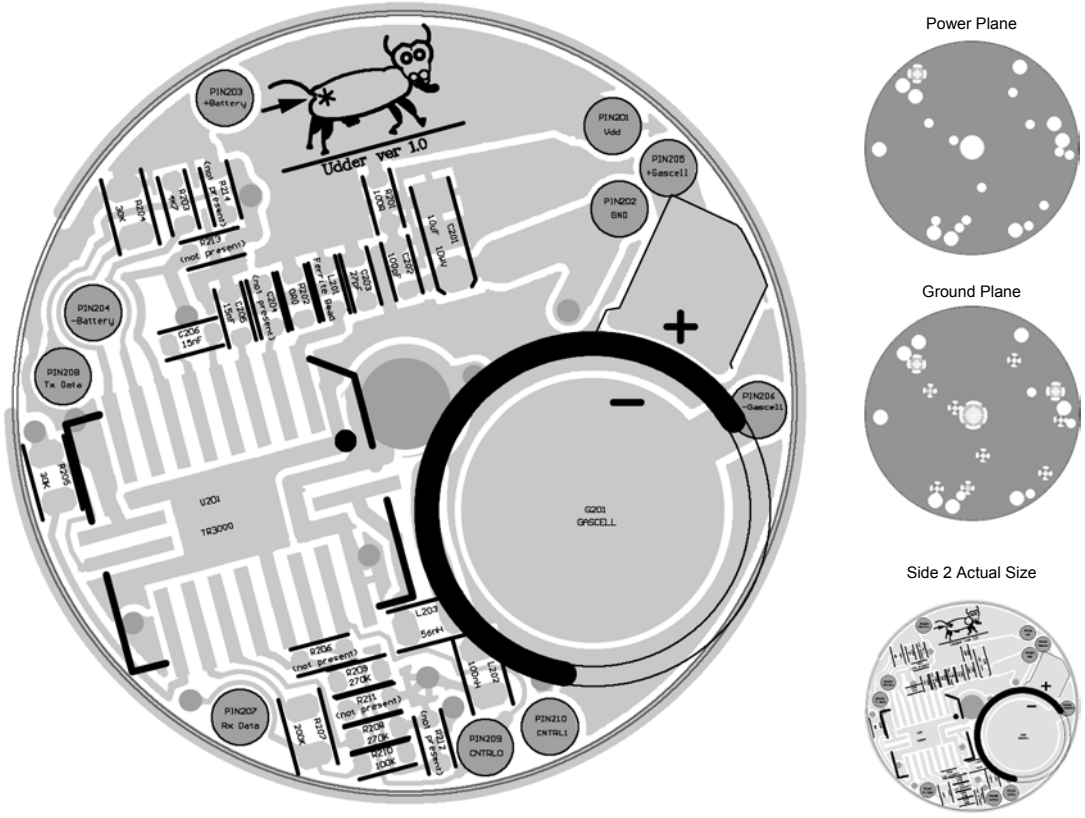


Figure 59: DMU PCB Layout: Transceiver and Batteries Board Side 2, Power and Ground Planes

Appendix D: DMU Bill of Materials

Table 11: DMU Bill of Materials

Designator	Description	Part Type	Foot-print	Manf. Part Number	Manufacturer	Supplier	Supplier Order Code	Top-mark	Comment	Function	Cost (Ex GST) NZ$
B201	Battery, button cell, 1.5V, Energizer brand, silver oxide, EPX76		11.5mm Diameter Button Cell	EPX76	Energizer	Cory's Electrical Wholesaler	EPX76	EPX76	Or other equivalent silver oxide battery	Electronics power supply, 1 of 3	$3.38
B202	Battery, button cell, 1.5V, Energizer brand, silver oxide, EPX76		11.5mm Diameter Button Cell	EPX76	Energizer	Cory's Electrical Wholesaler	EPX76	EPX76	Or other equivalent silver oxide battery	Electronics power supply, 2 of 3	$3.38
B203	Battery, button cell, 1.5V, Energizer brand, silver oxide, EPX76		11.5mm Diameter Button Cell	EPX76	Energizer	Cory's Electrical Wholesaler	EPX76	EPX76	Or other equivalent silver oxide battery	Electronics power supply, 3 of 3	$3.38
C101	Capacitor, 100nF, X7R, 16V, SMD, Ceramic,	100nF	0603		Philips Components -	Farnell	432-210			MCU power supply decoupling	$0.17
C102	Capacitor, 100nF, X7R, 16V, SMD, Ceramic,	100nF	0603		Philips Components -	Farnell	432-210			MCU AVss pin decoupling	$0.17
C103	Capacitor, 8.2pF, 5%, NPO, SMD, Ceramic,	8.2pF	0603		Philips Components	Farnell	721-955			For 32kHz MCU sub-clock	$0.13
C104	Capacitor, 8.2pF, 5%, NPO, SMD, Ceramic,	8.2pF	0603		Philips Components	Farnell	721-955			For 32kHz MCU sub-clock	$0.13
C105	Capacitor, 100nF, X7R, 16V, SMD, Ceramic,	100nF	0603		Philips Components -	Farnell	432-210			Decoupling for Vref on MCU	$0.17
C106	Capacitor, 6.8pF, 5%, NPO, SMD, Ceramic,	6.8pF	0603		Philips Components	Farnell	721-943			load for MCU main clock	$0.13
C107	Capacitor, 6.8pF, 5%, NPO, SMD, Ceramic,	6.8pF	0603		Philips Components	Farnell	721-943			load for MCU main clock	$0.13
C108	Capacitor, 100nF, X7R, 16V, SMD, Ceramic,	100nF	0603		Philips Components -	Farnell	432-210			Noise filter for gascell voltage measure	$0.17
C109	Capacitor, 100nF, X7R, 16V, SMD, Ceramic,	100nF	0603		Philips Components -	Farnell	432-210			Power supply decoupling for gascell monitor	$0.17
C110	Capacitor, 100nF, X7R, 16V, SMD, Ceramic,	100nF	0603		Philips Components -	Farnell	432-210			Part of low pass filter for gascell current accumulator measurements	$0.17
C111	Capacitor, 100nF, X7R, 16V, SMD, Ceramic,	100nF	0603		Philips Components -	Farnell	432-210			Power decoupling for pressure sensor	$0.17

Designator	Description	Part Type	Foot-print	Manf. Part Number	Manufacturer	Supplier	Supplier Order Code	Top-mark	Comment	Function	Cost (Ex GST) NZ$
C112	Capacitor, 100nF, X7R, 16V, SMD, Ceramic,	100nF	0603		Philips Components -	Farnell	432-210			Decoupling for LDR light indication voltage measure	$0.17
C113	Capacitor, 100nF, X7R, 16V, SMD, Ceramic,	100nF	0603		Philips Components -	Farnell	432-210			sets time delay between power fail indication and reset signal	$0.17
C114	Capacitor, 10uF, 10V, Tantalum, SMD, case size A, ESR = 3 OHMS@100Hz, 3.2x1.6mm	10uF 10WV	CAP-A	TAJA106K 010X	AVX	Farnell	197-130			Input capacitor for voltage regulators	$0.97
C115	Capacitor, 15nF, SMD, 5%, NPO, Ceramic,	15nF	0603		Philips Components	Farnell	722-248			Bypass capacitor for TC1073 3.0V regulator	$0.16
C116	Capacitor, 10uF, 10V, Tantalum, SMD, case size A, ESR = 3 OHMS@100Hz, 3.2x1.6mm	10uF 10WV	CAP-A	TAJA106K 010X	AVX	Farnell	197-130			Output capacitor for voltage regulators	$0.97
C117	Capacitor, 47uF, 4V, tantalum, SMD, case size B, ESR = 2.4 OHMS@100Hz, 3.5x2.8mm	47uF 4WV	CAP-B	TAJB476K 004X	AVX	Farnell	196-964			Power supply filtering on output of 3.0V regulator	$1.45
C201	Capacitor, 10uF, 10V, Tantalum, SMD, case size A, ESR = 3 OHMS@100Hz, 3.2x1.6mm	10uF 10WV	CAP-A	TAJA106K 010X	AVX	Farnell	197-130			Transceiver power supply decoupling	$0.97
C202	Capacitor, 100pF, 5%, NPO, SMD, Ceramic,	100pF	0603		Philips Components	Farnell	722-080			Crfb2 - Transceiver power supply decoupling	$0.14
C203	Capacitor, 27pF, SMD, 5%, NPO, Ceramic,	27pF	0603		Philips Components	Farnell	722-017			TXR Crfb1 - Transceiver power supply decoupling	$0.13
C204	Capacitor	not present	0603							Not fitted in OOK operation. Controls AGC operation when AGCCAP pin not tied to Vdd	$0.00
C205	Capacitor, 15nF, SMD, 5%, NPO, Ceramic,	15nF	0603		Philips Components	Farnell	722-248			Cpkd - peak detect attack and decay setting times	$0.16
C206	Capacitor, 15nF, SMD, 5%, NPO, Ceramic,	15nF	0603		Philips Components	Farnell	722-248			Cbbout - base band out to comparator in capacitor	$0.16
D101	LED, Dual red/green, SMD, 3×2·1mm	LSG T670-HK	T670	LSG T670-HK	Siemens/Infineon Technologies	Farnell	250-867			User feedback indicator	$2.12
D201	Diode, Switching, Schottky barrier, 200mA max, forward V drop @ 100uA = 240mV	BAT254	SOD110	BAT254	Philips Semiconductors	RS	216-9274	bar at cathode		Protects against reverse external voltage	$2.33
F101	Fuse, 125mA, FF (very fast acting)	125mA, FF	1206	429.125	LittelFuse	RS	283-0308	FB	Blows after approx. 5s at 250mA, or 0.1s at 300mA	Protects against over voltage and reverse voltage when Zener conducts.	$0.62

Designator	Description	Part Type	Foot-print	Manf. Part Number	Manufacturer	Supplier	Supplier Order Code	Top-mark	Comment	Function	Cost (Ex GST) NZ$
G201	Gascell, 11.6mm diameter	GASCELL	11.5mm Diameter Button Cell	gascell, 11.6mm diameter, 5.4mm height, 150mL	Simatec		gascell, 11.6mm diameter, 5.4mm height, 150mL	two small holes	Approximate price	Gascell. Releases hydrogen gas under load to drive syringe piston	$3.00
H101	Header for optional installation of jumper, 0.1 inch spacing	HEADER	CON - SIL2 - NARROW			RS	227-2639		price is for 2 pins of the 32 way break-off strip and one jumper.	General IO connector	$1.08
H102	Header replaced by SPST, SMD DIP switch	DIP1	CON - SIL2	CHS-01 B	NIDEC Copal Electronics	RS	352-4818			For selecting program or run MCU boot mode	$3.82
J101	Connector, made from 1 socket and 1 pin of a SIL strip	SIL2	CON - SIL2			RS	267-7416, 227-2639		Price is for one socket and one pin. 32 way socket strip: 267-7416, 32 way socket strip: RS 227-2639	Aux comm port connector	$0.32
J102	Connector, made from 1 socket and 3 pins of a SIL strip	SIL4	CON - SIL4			RS	267-7416, 227-2639		Price is for 3 sockets and 1 pin. 32 way socket strip: 267-7416, 32 way socket strip: RS 227-2639	Hardware debugging and serial programming port connector	$0.48
J201	Connector, made from 1 socket and 1 pin of a SIL strip	SIL2	CON - SIL2			RS	267-7416, 227-2639		Price is for one socket and one pin. 32 way socket strip: 267-7416, 32 way socket strip: RS 227-2639	External power connector	$0.32
L101	Ferrite Bead, Inductor, chip, , Impedance 120,DCR OHM,0.8, MA 200	Ferrite Bead	0603	2506031217YOD	Fair-Rite	Allied Electronics	589-0552			MCU power supply filtering	$0.34
L201	Ferrite Bead, Inductor, chip, , Impedance 120,DCR OHM,0.8, MA 200	Ferrite Bead	0603	2506031217YOD	Fair-Rite	Allied Electronics	589-0552			TXR Lrfb - Transceiver power supply filtering	$0.34
L202	Inductor 100nH, 5%, SMD 0805 package	100nH	0805	0805CS-101XJBB	Coilcraft	Coilcraft	0805CS-101XJBB	white dot	price is approximate	Lesd - parallel tuning and ESD protection for RFIO pin	$1.00
L203	Inductor, 56nH, 5%, SMD 0805 package	56nH	0805	0805CS-560XJBB	Coilcraft	Coilcraft	0805CS-560XJBB		price is approximate	Lat - antenna tuning series inductor	$1.00
PIN201	Connector, 1 pin SIL header pin strip, single row straight, 32 way, circular cross section	PIN: Vdd	CON-PIN1FP			RS	227-2639		price is for 1 pin of the 32 way break-off strip	Vdd PCB interconnect	$0.24
PIN202	Connector, 1 pin SIL header pin strip, single row straight, 32 way, circular cross section	PIN: GND	CON-PIN1FP			RS	227-2639		price is for 1 pin of the 32 way break-off strip	GND PCB interconnect	$0.24

Designator	Description	Part Type	Foot-print	Manf. Part Number	Manufacturer	Supplier	Supplier Order Code	Top-mark	Comment	Function	Cost (Ex GST) NZ$
PIN203	Connector, 1 pin SIL header pin strip, single row straight, 32 way, circular cross section	PIN: +Battery	CON-PIN1FP			RS	227-2639		price is for 1 pin of the 32 way break-off strip	+Battery PCB interconnect	$0.24
PIN204	Connector, 1 pin SIL header pin strip, single row straight, 32 way, circular cross section	PIN: -Battery	CON-PIN1FP			RS	227-2639		price is for 1 pin of the 32 way break-off strip	-Battery PCB interconnect	$0.24
PIN205	Connector, 1 pin SIL header pin strip, single row straight, 32 way, circular cross section	PIN: +Gascell	CON-PIN1FP			RS	227-2639		price is for 1 pin of the 32 way break-off strip	+Gascell PCB interconnect	$0.24
PIN206	Connector, 1 pin SIL header pin strip, single row straight, 32 way, circular cross section	PIN: -Gascell	CON-PIN1FP			RS	227-2639		price is for 1 pin of the 32 way break-off strip	-Gascell PCB interconnect	$0.24
PIN207	Connector, 1 pin SIL header pin strip, single row straight, 32 way, circular cross section	PIN: Rx Data	CON-PIN1FP			RS	227-2639		price is for 1 pin of the 32 way break-off strip	Rx Data PCB interconnect	$0.24
PIN208	Connector, 1 pin SIL header pin strip, single row straight, 32 way, circular cross section	PIN: Tx Data	CON-PIN1FP			RS	227-2639		price is for 1 pin of the 32 way break-off strip	Tx Data PCB interconnect	$0.24
PIN209	Connector, 1 pin SIL header pin strip, single row straight, 32 way, circular cross section	PIN: CNTRL0	CON-PIN1FP			RS	227-2639		price is for 1 pin of the 32 way break-off strip	CNTRL0 PCB interconnect	$0.24
PIN210	Connector, 1 pin SIL header pin strip, single row straight, 32 way, circular cross section	PIN: CNTRL1	CON-PIN1FP			RS	227-2639		price is for 1 pin of the 32 way break-off strip	CNTRL1 PCB interconnect	$0.24
R101	Resistor, 270R, SMT, Format, 1% tol, 0.1W	270R	0603	CRG0603 Series	Neoohm	RS	213-2193	271		Provides load for voltage droop test	$0.05
R102	Resistor, 10K, SMT, Format, 1% tol, 0.1W	10K	0603	CRG0603 Series	Neoohm	RS	213-2418	103		For boot/monitor program	$0.05
R103	Resistor, 10K, SMT, Format, 1% tol, 0.1W	10K	0603	CRG0603 Series	Neoohm	RS	213-2418	103		For boot/monitor program	$0.05
R104	Resistor	not present	0603							Pull down for MCU pin as required by boot loader	$0.00
R105	Resistor, 10K, SMT, Format, 1% tol, 0.1W	10K	0603	CRG0603 Series	Neoohm	RS	213-2418	103		Pull down for MCU CLK1 pin as required by boot loader	$0.05
R106	Resistor, 10K, SMT, Format, 1% tol, 0.1W	10K	0603	CRG0603 Series	Neoohm	RS	213-2418	103		Pull-up up for TxD2 - open drain	$0.05
R107	Resistor, 10K, SMT, Format, 1% tol, 0.1W	10K	0603	CRG0603 Series	Neoohm	RS	213-2418	103		Pull-up up for RxD2 - open drain	$0.05
R108	Resistor	not present	0603							For optional connection of TXR - Tx Data to TxD2	$0.00
R109	Resistor	not present	0603							For optional connection of TXR - Rx Data to RxD2	$0.00

Designator	Description	Part Type	Foot-print	Manf. Part Number	Manufacturer	Supplier	Supplier Order Code	Top-mark	Comment	Function	Cost (Ex GST) NZ$
R110	Resistor, 0R0, SMT, Format, 1% tol, 0.1W	0R0	0603	CRG0603 Series	Neoohm	RS	213-1982	0		For optional connection of TXR - Rx Data to INT0	$0.05
R111	Resistor, 0R0, SMT, Format, 1% tol, 0.1W	0R0	0603	CRG0603 Series	Neoohm	RS	213-1982	0		For optional connection of TXR - Rx Data to INT0	$0.05
R112	Resistor, 10K, SMT, Format, 1% tol, 0.1W	10K	0603	CRG0603 Series	Neoohm	RS	213-2418	103		Pull up for MCU NMI pin	$0.05
R113	Resistor	not present	0603							Was power fail signal to MCU NMI pin - but manual says not to reset MCU when NMI low	$0.00
R114	Resistor, 10K, SMT, Format, 1% tol, 0.1W	10K	0603	CRG0603 Series	Neoohm	RS	213-2418	103		pull down for MCU CNVss pin	$0.05
R115	Resistor, 1M, SMT, Format, 1% tol, 0.1W	1M	0603	CRG0603 Series	Neoohm	RS	213-2676	105		Holds RxD0 line low to prevent floating. Must be kept an input line so that interrupt can occur in sleep mode.	$0.05
R116	Resistor, 1M, SMT, Format, 1% tol, 0.1W	1M	0603	CRG0603 Series	Neoohm	RS	213-2676	105		TxD0 ESD protection.	$0.05
R117	Resistor, 1M, SMT, Format, 1% tol, 0.1W	1M	0603	CRG0603 Series	Neoohm	RS	213-2676	105		Holds RxD1 line low to prevent floating. Must be kept an input line so that interrupt can occur in sleep mode.	$0.05
R118	Resistor, 1M, SMT, Format, 1% tol, 0.1W	1M	0603	CRG0603 Series	Neoohm	RS	213-2676	105		TxD1 ESD protection.	$0.05
R119	Resistor	not present	0603							Pull-up for DQ line on gascell monitor - internal MCU pull up used instead.	$0.00
R120	Resistor, 1M, SMT, Format, 1% tol, 0.1W	1M	0603	CRG0603 Series	Neoohm	RS	213-2676	105		Pull down resistor for tilt switch to minimize current flow into MCU IO pin	$0.05
R121	Resistor, 3R9, SMT, 0805 Format, 2% tol, 0.1W	3R9	0805	RL73 Series	Meggitt Polymers & Composites	Farnell	310-4540	3R9	Farnell Feb 2000 catalogue page 1717	Sense resistor for measuring gascell current	$1.11
R122	Resistor, 100K, SMT, Format, 1% tol, 0.1W	100K	0603	CRG0603 Series	Neoohm	RS	213-2531	104		Part of low pass filter for gascell current accumulator measurements	$0.05
R123	Resistor, 0R0, SMT, Format, 1% tol, 0.1W	0R0	0603	CRG0603 Series	Neoohm	RS	213-1982	0		Facilitates gascell current measurements when bench testing	$0.05
R124	Resistor, 10R, SMT, Format, 1% tol, 0.1W	10R	0603	CRG0603 Series	Neoohm	RS	213-2008	10R		Gascell load - dissipates 100mW max	$0.05
R126	Resistor, 270R, SMT, Format, 1% tol, 0.1W	270R	0603	CRG0603 Series	Neoohm	RS	213-2193	271		Current limit for red LED	$0.05
R127	Resistor, 270R, SMT, Format, 1% tol, 0.1W	270R	0603	CRG0603 Series	Neoohm	RS	213-2193	271		Current limit for green LED	$0.05

Designator	Description	Part Type	Foot-print	Manf. Part Number	Manufacturer	Supplier	Supplier Order Code	Top-mark	Comment	Function	Cost (Ex GST) NZ$
R128	Light Dependent Resistor, Miniature, cadmium sulphide, TO18 package	LDR	LDR	NSL19-MS51		RS	596-141			Sensor for light level indication	$2.89
R129	Resistor, 1M, SMT, Format, 1% tol, 0.1W	1M	0603	CRG0603 Series	Neoohm	RS	213-2676	105		Pull down resistor for LDR to minimize current flow into MCU IO pin	$0.05
R130	Resistor, 15K, SMT, Format, 1% tol, 0.1W	15K	0603	CRG0603 Series	Neoohm	RS	213-2430	153		sets time delay between power fail indication and reset signal	$0.05
R131	Resistor	not present	0603							If the TC1073 is the only regulator fitted, this 0R0 resistor ensures that the regulator is always enabled. In that case disconnect Vreg shutdown, else it will be connected to greater than the MCU's Vdd.	$0.00
R132	Resistor, 0R0, SMT, Format, 1% tol, 0.1W	0R0	0603	CRG0603 Series	Neoohm	RS	213-1982	0		Top trim resistor for supervisor reset threshold sense	$0.05
R133	Resistor, 1M, SMT, Format, 1% tol, 0.1W	1M	0603	CRG0603 Series	Neoohm	RS	213-2676	105		Top main resistor for supervisor reset threshold sense	$0.05
R134	Resistor, 1M, SMT, Format, 1% tol, 0.1W	1M	0603	CRG0603 Series	Neoohm	RS	213-2676	105		Bottom resistor for supervisor reset threshold sense	$0.05
R135	Resistor, 2R2, SMT, 0805 Format, 2% tol, 0.1W	2R2	0805	RL73 Series	Meggitt Polymers & Composites	Farnell	213-2418	2R2	Farnell Feb 2000 catalogue page 1717	Current sense resistor for batteries that power the electronics	$1.11
R136	Resistor, 1M, SMT, Format, 1% tol, 0.1W	1M	0603	CRG0603 Series	Neoohm	RS	213-2676	105		Connects open drain error output on TC1073 3.0V regulator to maintain correct output when in shutdown mode	$0.05
R201	Resistor, 100R, SMT, Format, 1% tol, 0.1W	100R	0603	CRG0603 Series	Neoohm	RS	213-2143	101		Rrfb - Transceiver power supply filtering	$0.05
R202	Resistor, 0R0, SMT, Format, 1% tol, 0.1W	0R0	0603	CRG0603 Series	Neoohm	RS	213-1982	0		TXR - to tie AGCCAP high	$0.05
R203	Resistor, 4K7, SMT, Format, 1% tol, 0.1W	4K7	0603	CRG0603 Series	Neoohm	RS	213-2367	472		Rtxm - alters transmitter output power	$0.05
R204	Resistor, 30K, SMT, 0805 Format, 5% tol, 0.1W	30K	0805		MultiComp	Farnell	771-510	303	Farnell Feb 2000 catalogue page 1715	Rlfp - LPFADJ resistor - receiver low pass filter bandwidth adjust	$0.11
R205	Resistor, 30K, SMT, 0805 Format, 5% tol, 0.1W	30K	0805		MultiComp	Farnell	771-510	303	Farnell Feb 2000 catalogue page 1715	Rth2 - sets DS2 data slicer trip point	$0.11
R206	Resistor	not present	0603							Not fitted in OOK design - Minimizes power consumption in sleep mode when using ASK (page 39 of designer's Guide)	$0.00

Designator	Description	Part Type	Foot-print	Manf. Part Number	Manufacturer	Supplier	Supplier Order Code	Top-mark	Comment	Function	Cost (Ex GST) NZ$
R207	Resistor, 200K, SMT, 0805 Format, 5% tol, 0.1W	200K	0805		MultiComp	Farnell	771-612	204	Farnell Feb 2000 catalogue page 1715	Rth1 - heps set squelch and threshold for the standard data slicer	$0.11
R208	Resistor, 270K, SMT, Format, 1% tol, 0.1W	270K	0603	CRG0603 Series	Neoohm	RS	213-2597	271		Rpr - PRATE resistor - sets interval between the falling and rising edge of an ON pulse to the first RF amplifier	$0.05
R209	Resistor, 270K, SMT, Format, 1% tol, 0.1W	270K	0603	CRG0603 Series	Neoohm	RS	213-2597	271		Rpw - PWIDTH resistor - width of the ON pulse to the first RF amplifier	$0.05
R210	Resistor, 100K, SMT, Format, 1% tol, 0.1W	100K	0603	CRG0603 Series	Neoohm	RS	213-2531	104		Rref - helps set squelch	$0.05
R211	Resistor	not present	0603							Not required	$0.00
R212	Resistor	not present	0603							Not required	$0.00
R213	Resistor	not present	0603							Would stop this line floating in sleep and transmit modes, but the MCU outputs a low to do that so not required	$0.00
R214	Resistor	not present	0603							Not required	$0.00
S101	Tilt switch, non-mercury, max diff angle = 15 degrees.	RS 235-7639	TILT SWITCH			RS	235-7639			Senses mounting activity of cow	$12.89
S102	Switch, SPST, momentary action, 4.8x5.0mm, SMD, 24V, 100mA	Manual Reset	SPST MOMENTARY ACTION	7914J-001-000	Bourns	Farnell	535-930			Resets MCU	$2.52
SOCKET101	Connector, 1 socket of wire wrap SIL socket pin strip, single row straight, 32 way, circular cross section	SOCKET: Vdd	CON-PIN1FP			RS	267-7444		price is for 1 socket of the 32 way break-off strip	Vdd PCB interconnect	$0.25
SOCKET102	Connector, 1 socket of wire wrap SIL socket pin strip, single row straight, 32 way, circular cross section	SOCKET: GND	CON-PIN1FP			RS	267-7444		price is for 1 socket of the 32 way break-off strip	GND PCB interconnect	$0.25
SOCKET103	Connector, 1 socket of wire wrap SIL socket pin strip, single row straight, 32 way, circular cross section	SOCKET: +Battery	CON-PIN1FP			RS	267-7444		price is for 1 socket of the 32 way break-off strip	+Battery PCB interconnect	$0.25
SOCKET104	Connector, 1 socket of wire wrap SIL socket pin strip, single row straight, 32 way, circular cross section	SOCKET: -Battery	CON-PIN1FP			RS	267-7444		price is for 1 socket of the 32 way break-off strip	-Battery PCB interconnect	$0.25
SOCKET105	Connector, 1 socket of wire wrap SIL socket pin strip, single row straight, 32 way, circular cross section	SOCKET: +Gascell	CON-PIN1FP			RS	267-7444		price is for 1 socket of the 32 way break-off strip	+Gascell PCB interconnect	$0.25

Designator	Description	Part Type	Foot-print	Manf. Part Number	Manufacturer	Supplier	Supplier Order Code	Top-mark	Comment	Function	Cost (Ex GST) NZ$
SOCKET106	Connector, 1 socket of wire wrap SIL socket pin strip, single row straight, 32 way, circular cross section	SOCKET: -Gascell	CON-PIN1FP			RS	267-7444		price is for 1 socket of the 32 way break-off strip	-Gascell PCB interconnect	$0.25
SOCKET107	Connector, 1 socket of wire wrap SIL socket pin strip, single row straight, 32 way, circular cross section	SOCKET: Rx Data	CON-PIN1FP			RS	267-7444		price is for 1 socket of the 32 way break-off strip	Rx Data PCB interconnect	$0.25
SOCKET108	Connector, 1 socket of wire wrap SIL socket pin strip, single row straight, 32 way, circular cross section	SOCKET: Tx Data	CON-PIN1FP			RS	267-7444		price is for 1 socket of the 32 way break-off strip	Tx Data PCB interconnect	$0.25
SOCKET109	Connector, 1 socket of wire wrap SIL socket pin strip, single row straight, 32 way, circular cross section	SOCKET: CNTRL0	CON-PIN1FP			RS	267-7444		price is for 1 socket of the 32 way break-off strip	CNTRL0 PCB interconnect	$0.25
SOCKET110	Connector, 1 socket of wire wrap SIL socket pin strip, single row straight, 32 way, circular cross section	SOCKET: CNTRL1	CON-PIN1FP			RS	267-7444		price is for 1 socket of the 32 way break-off strip	CNTRL1 PCB interconnect	$0.25
U101	M16C microcontroller from Mitsubishi - LQFP square package: 100P6Q-A	M30624FGLGP	LQFP100-P-1414-0.50 - MISSING PADS	M30624FGLGP	Mitsubishi	Mitsubishi Electric Australia	M30624FGLGP	M30624FGLGP		Controls all functions son DMU	$35.00
U102	Smart Battery Monitor IC - symbol for X reflected placement on schematic	DS2438	SOIC-8 - MISSING PADS	DS2438	Dallas Semiconductor	Memec	DS2438	DS2438		Integrates current from gascell, measures pre-reg and Vdd voltage. Digital 1-wire serial interface	$5.11
U103	SPST Analogue switch	MAX4628	SOT23-6	MAX4628	Maxim	Power Technology Components Ltd	MAX4628	AADN		Switches low rate load for gascell on and off	$3.51
U104	Pressure Sensor Module with serial interface	MS5535A	MS5535AM - BUMP IN HOLE	MS5535AM	Intersema Sensoric SA	Intersema Sensoric SA	MS5535AM	-blank-	Do not exceed 225C. Do not heat for longer than 30 seconds.	Pressure and temperature sensor	$63.18
U106	MCU supervisory reset IC	MAX6308	SOT23-5	MAX6308-UK00D3-T	Maxim	Maxim	MAX6308-UK00D3-T	ABIQ	Approximate price given	Provides power fail and reset signal when Vdd drops too low	$3.00
U107	Voltage Regulator, 3.0V, 80mA, 1.1uA quiescent current	MC78FC30HT1	SOT89	MC78FC30HT1	Motorola	RS	246-7843	OK GT		3.0V regulator with low 1.1uA quiescent current	$4.34
U108	Voltage Regulator, 3.0V, 100mA	TC1073-30VCH	SOT23-6	TC1073-30VCT	TelCom	Farnell	119-301	F3FA		3.0V regulator with low voltage differential	$8.83
U201	Transceiver, Amplifier Sequenced Hybrid, 433.93MHz	TR3000	SM-20L	TR3000	RF Monolithics	Megtech	TR3000		Alternate supplier: Insight Electronics	Transceiver sends and receives data via RF under control of the MCU	$62.25

Designator	Description	Part Type	Foot-print	Manf. Part Number	Manufacturer	Supplier	Supplier Order Code	Top-mark	Comment	Function	Cost (Ex GST) NZ$
W201	PCB pad for direct mounting of semi-rigid co-ax	CO-AX MOUNT PAD	CO-AX MOUNT							Special PCB pad to mount transceiver transmission line semi-rigid co-ax directly	$0.00
Y101	Crystal, 32.768kHz, 8.2pF load capacitance, 20ppm	32.768kHz	DS10	DS10-0N	Micro Crystal Switzerland	Micro Crystal Switzerland	DS10-0N		Do not exceed 280C. Do not heat for more than 5sec. Do not solder can. Price is approximate.	32kHz MCU sub-clock	$5.00
Y102	Crystal, 10.000 MHz, 6.8pF load capacitance, RSX-3, 30ppm	10.000MHz	RSX-3	DHE08RSX-3 10.0 MHz	Rakon	Rakon	DHE08RSX-3 10.0 MHz	10.00M 0400N1	Able to withstand reflow soldering.	10.000MHz main clock	$15.00
Z101	Zener Diode, 6.2V	6V2	SOT23	BXZ84C6V2	Philips Semiconductors	Farnell	251-604	Z60 or Z4P or Z4T		Helps protect voltage regulators from input over voltage.	$0.46
								Total Component Cost (Ex GST)			$264.36

Appendix E: Base Station/Development DMU

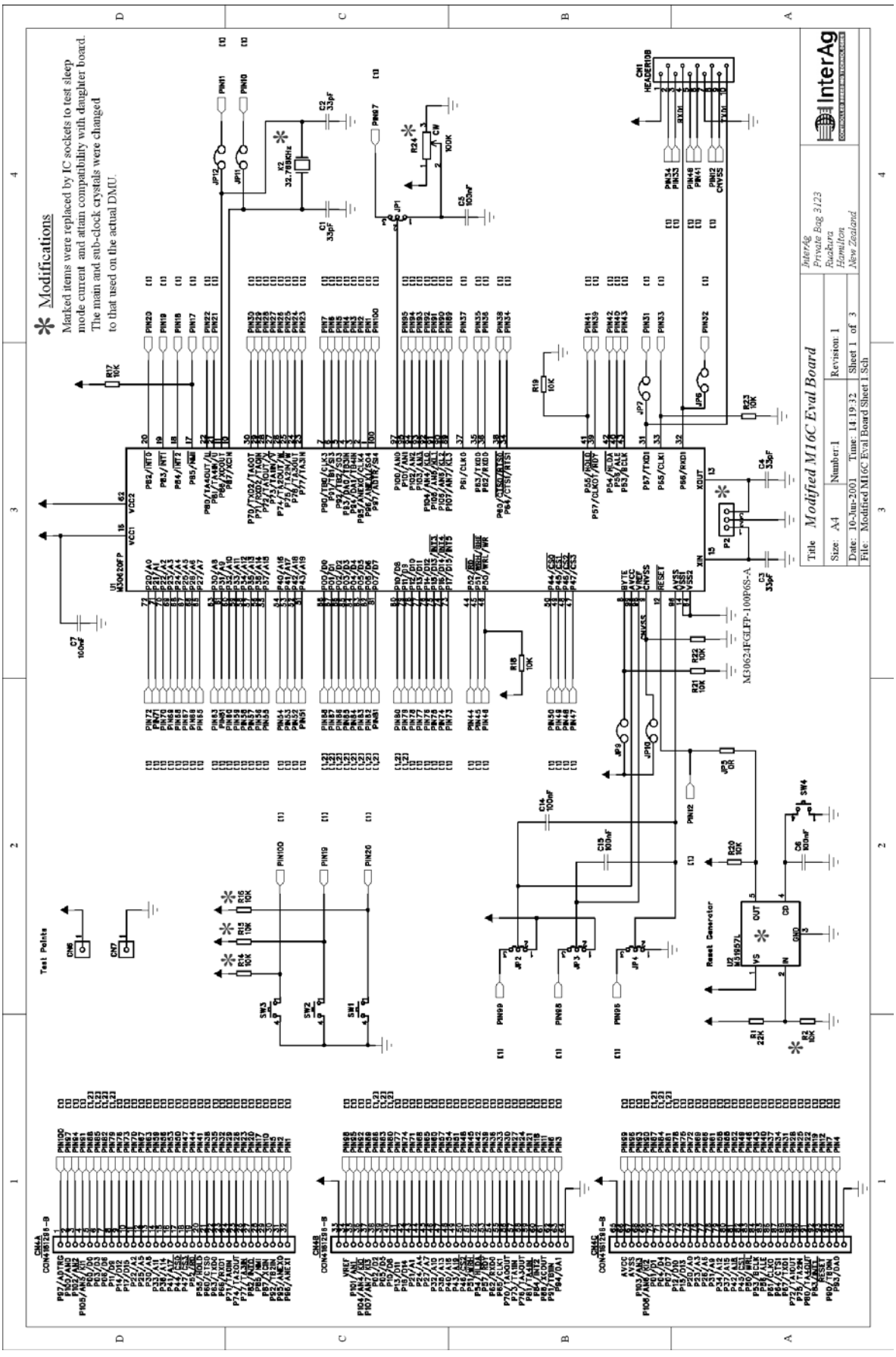


Figure 60: Modified M16C Evaluation Board Schematic — Sheet 1

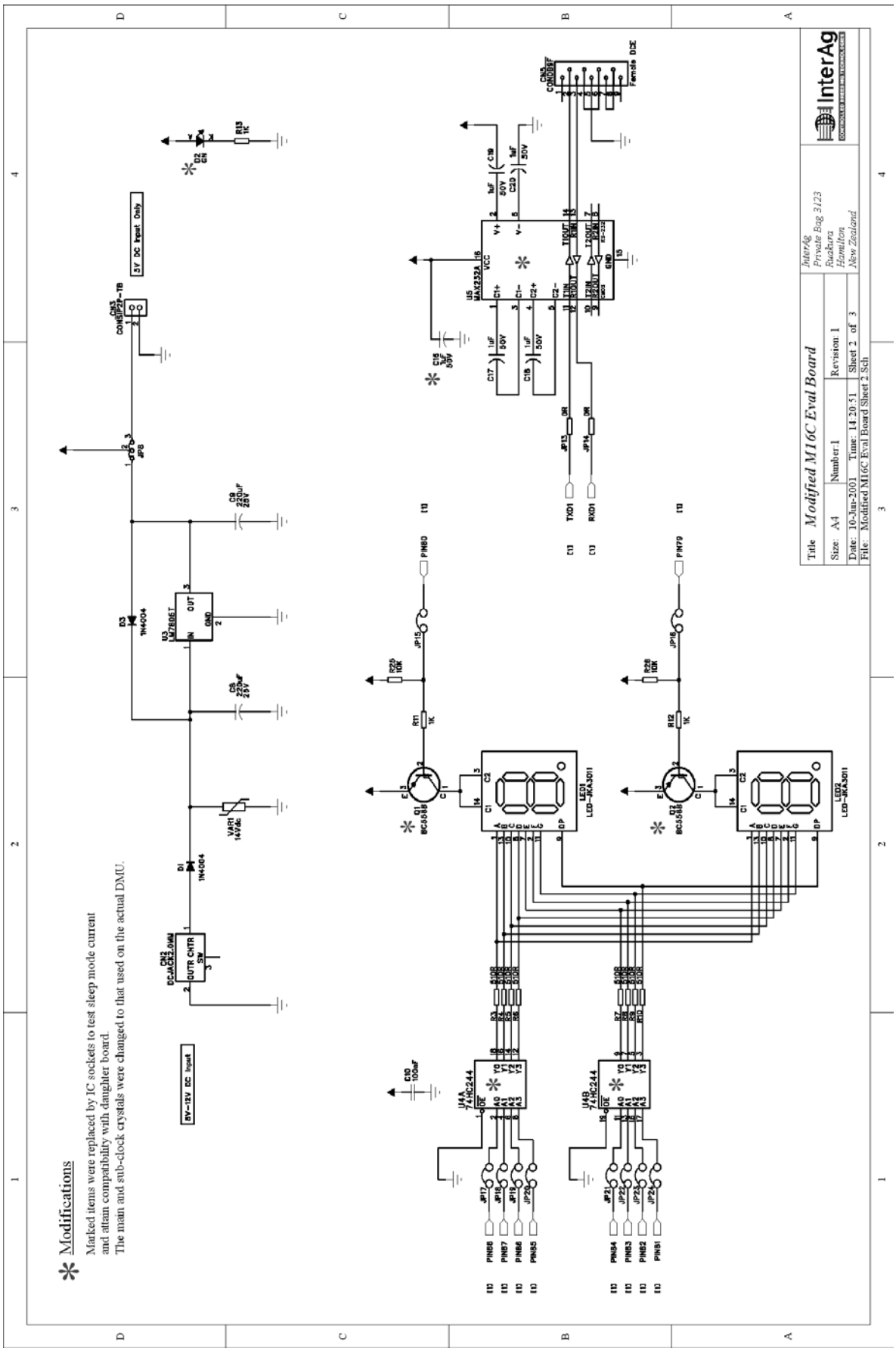


Figure 61: Modified M16C Evaluation Board Schematic — Sheet 2

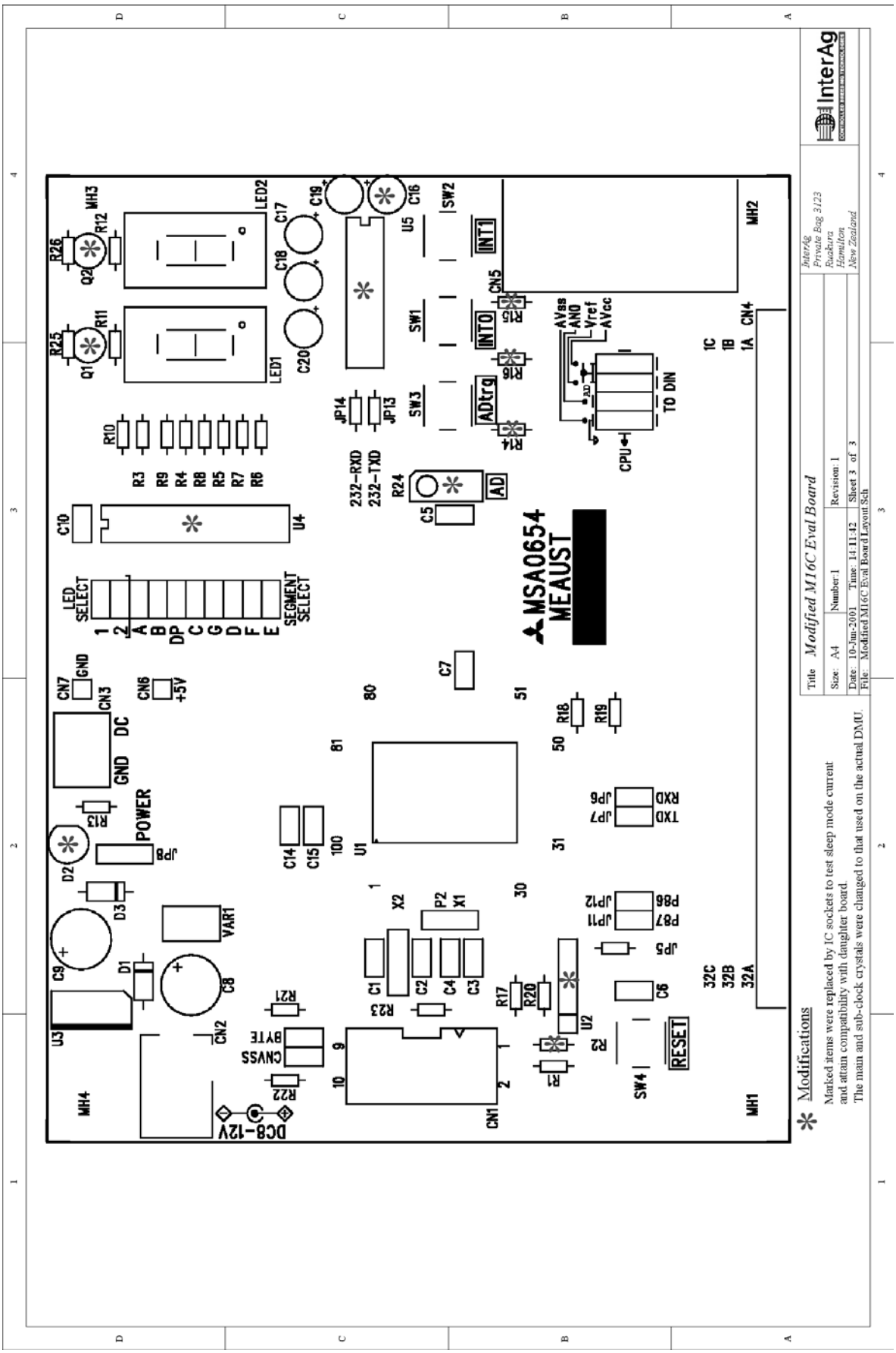


Figure 62: Modified M16C Evaluation Board PCB Layout

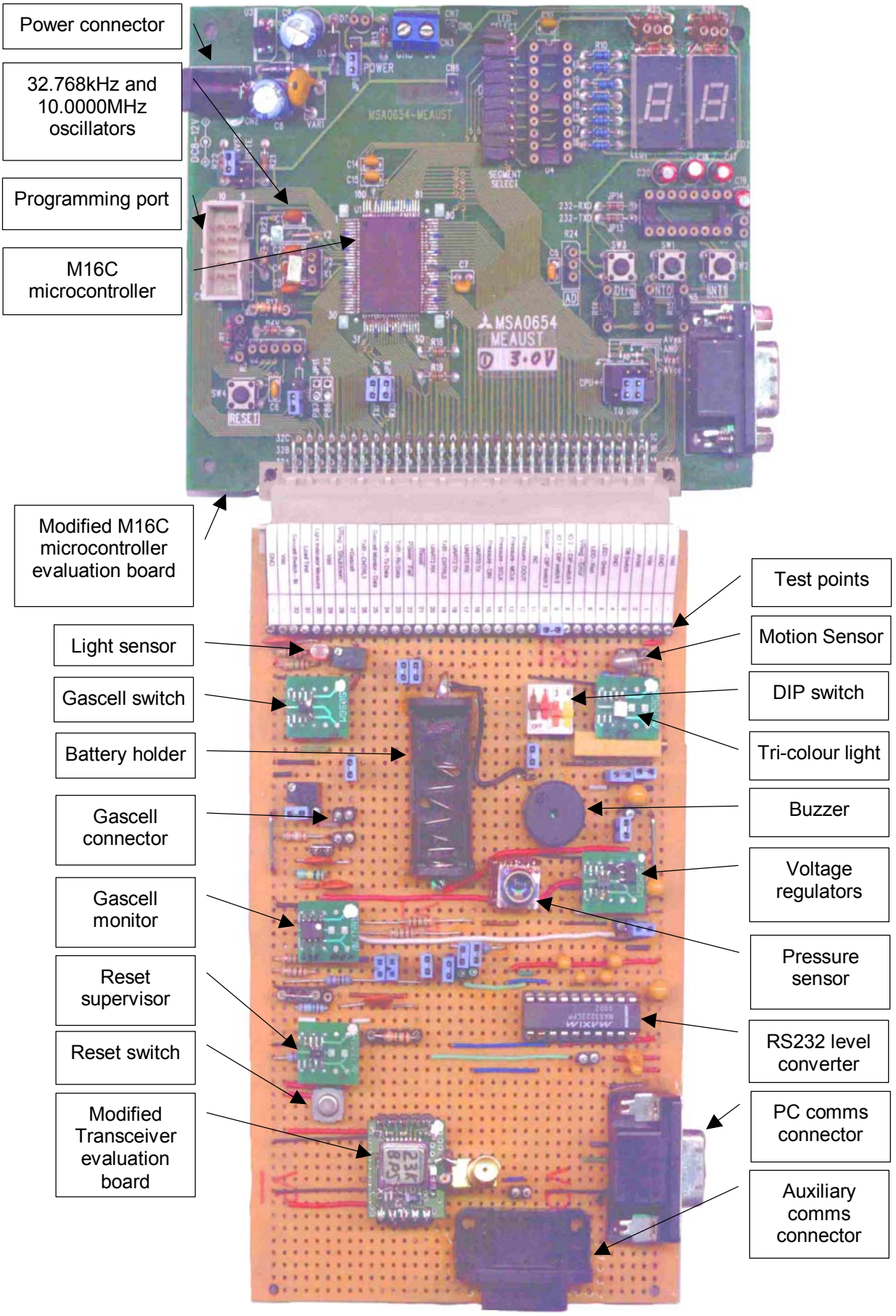


Figure 63: Base Station/Development DMU

Table 12: Development Board Cross Reference Wiring Table

MCU Alternate Pin Allocation								MCU Primary Pin Allocation				Daughter Board	
MCU Pin Description	M30624FGLFP MCU Pin (Rectangle package)	M30624FGLGP MCU Pin (Square package)	DIN Connector Pin	MCU Pin Description	M30624FGLFP MCU Pin (Rectangle package)	M30624FGLGP MCU Pin (Square package)	DIN Connector Pin	MCU Pin Description	M30624FGLFP MCU Pin (Rectangle package)	M30624FGLGP MCU Pin (Square package)	DIN Connector Pin	Function	Test Point Pin
				Vcc	16	14	33	Vcc	62	60	65	Vdd	-
				Vss	14	62	64	Vss	64	12	96	GND	-
				Vcc	16	14	33	Vcc	62	60	65	Vdd	1
				Avcc	99	97	66	Vref	98	96	34	AVdd	2
P1.7/D15/INT5	73	71	10	P7.5/TA2in/W	25	23	90	P9.3/DA0/TB3in	4	2	95	Tilt Switch	3
				Vss	14	62	64	Vss	64	12	96	GND	4
								P3.5/A13	57	55	47	LED - Green	5
								P3.6/A14	56	54	15	LED - Red	6
								P1.6/D14/INT4	74	72	42	VReg - Error	7
								P2.0/A0	72	70	75	IO 2 - DIP switch 4	8
								P2.1/A1	71	69	43	IO 1 - DIP switch 3	9
								NC	NC	NC	NC	Buzzer - DIP switch 2	10
								NC	NC	NC	NC	NC	11
								P8.4/INT2	18	16	60	Pressure - DOUT	12
				P1.5/D13/INT3	75	73	74	P5.7/RDY/CLKout	39	37	53	Pressure - MCLK	13
								P8.0/TA4out/U	22	20	91	Pressure - SCLK	14
								P5.1/WRH/BHE	45	43	51	Pressure - DIN	15
								P6.3/TxD0	35	33	22	UART0 TX	16
								P6.2/RxD0	36	34	54	UART0 RX	17
								P7.0/TxD2/SDA/TA0out	30	28	56	UART2 TX	18
								P3.0/A8	63	61	13	TXR - CNTRL0	19
								P7.1/RxD2/SCL/TA0in/TB5in	29	27	24	UART2 RX	20
								RESET	12	10	93	Reset	21
								P8.3/INT1	19	17	92	Power Fail	22
P8.2/INT0	20	18	27	P7.3/CTS2/RTS2/TA1in/V	27	25	57	P6.2/RxD0	36	34	54	TXR - Rx Data	23
P7.2/CLK2/TA1out/V	28	26	89	P7.6/TA3out	24	22	58	P6.3/TxD0	35	33	22	TXR - Tx Data	24
				P4.1/A17	53	51	16	P4.2/A18	52	50	81	Gascell Monitor - Data	25
								P3.1/A9	61	59	78	TXR - CNTRL1	26
								P10.1/AN1	95	93	35	+Gascell	27
								P3.4/A12	58	56	79	Vreg - Shutdown	28
				Vcc	16	14	33	Vcc	62	60	65	Vdd	29
								P10.2/AN2	94	92	3	Light Indicator Measure	30
P2.4/A4	66	64	77	P2.5/A5	67	65	12	P2.6/A6	68	66	44	Load Test	31
								P9.1/TB1in/Sin3	6	4	62	Gascell Switch - IN	32
				Vcc	16	14	33	Vcc	62	60	65	Vdd	-
				Vss	14	62	64	Vss	64	12	96	GND	-

Settings for the M16C MCU Evaluation Board

There are two of these. One has been modified so that some components can be removed. This makes it pretty much 100% look like part of the circuit for the DMU. For example, the MAX232A IC can be removed so that it does not draw any current. This facilitates sleep mode power measurements where currents of only a few μA need to be measured accurately. To make this board as compatible as possible, remove all IC's and other components with sockets (except for the crystal) and configure the jumpers as follows before connecting to the Veroboard daughter board:

Table 13: Jumper Settings for the M16C Microcontroller Evaluation Board

Jumper	State	Comment
JP1	"to DIN" (bottom) setting	AN0
JP2	"to DIN" (bottom) setting	AVcc
JP3	"to DIN" (bottom) setting	Vref
JP4	Eval board Vss (top) setting	AVss
JP5	Open	MCU Reset
JP6	Closed	for RXD1 to DIN
JP7	Closed	for TXD1 to DIN
JP8	Open if powered from daughter board Closed if powered from eval board	Power source select. If this is left closed when operating from batteries, there will be around 50μA leakage through the electrolytic capacitors etc.
JP9	Closed	BYTE
JP10	Open or closed	Selects serial program download or run mode.
JP15 and JP 16	Open	LED digit select
JP17 to JP 24	Open	LED segment select

DR3100 Transceiver Module Modification

By default, the DR3100 transceiver modules are set up for 2.4k Bits Per Second (BPS) operation. To change them so they be can be used at the chosen bit rate of 23k BPS, the following changes were made:

Designator on DR3100 Datasheet	New Value	New Tolerance
C3	15nF	10%
R3	200K	1%
R6	30K	5%
R8	30K	5%
L2	100nH	10%

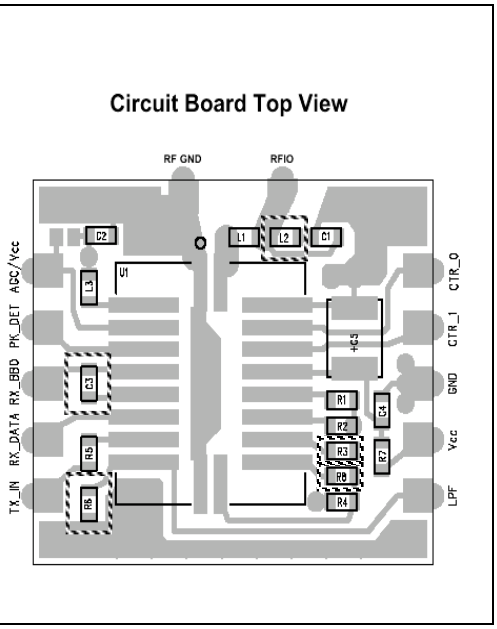


Figure 64: Modifications to DR3100 Transceiver Module

Appendix F: CD-ROM Contents

****	This thesis in PDF format (low resolution for online viewing).
\thesis	This thesis in Word for Windows and PDF format (high resolution for printing).
\thesis\web_page	This thesis as a web page.
\thesis\refs	References in Reference Manager 9 database format.
\cad_file	Schematic and PCB layout files in Protel 99 SE format
\data_sht	Data sheets and application notes for all components used in the DMU.
\results	Results downloaded from each cow into Excel format. This includes all raw data, processed data, graphs and explanations.
\source	The source code for the DMU and base station written in C for the M16C microcontroller using the Mitsubishi KNC30WA compiler.

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